



MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Zolgensma (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy (SMA)

Table of Contents

- [Policy: Commercial](#)
- [Policy: Medicare](#)
- [Authorization Information](#)
- [Coding Information](#)
- [Description](#)
- [Policy History](#)
- [Information Pertaining to All Policies](#)
- [References](#)

Policy Number: 008

BCBSA Reference Number: 5.01.28

NCD/LCD: N/A

Related Policies

- Spinal Muscular Atrophy (SMA) Medications, #044
- Prior Authorization Request Form for Zolgensma (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy (SMA), #085

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

ZolgensmaTM (onasemnogene abeparvovec-xioi) may be considered **MEDICALLY NECESSARY** if all of the following conditions are met:

1. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene as stated below:
 - a. Deletion of both copies of the *SMN1* gene; **OR**
 - b. Compound heterozygous mutations of the *SMN1* gene (defined below):
 - i. Pathogenic variant(s) in both copies of the *SMN1* gene; **OR**
 - ii. Pathogenic variant in 1 copy and deletion of the second copy of the *SMN1* gene; **AND**
2. Documentation of a genetic test confirms no more than 4 copies of the *SMN2* gene; **AND**
3. The individual is less than 2 years of age at the time of infusion of onasemnogene abeparvovec-xioi; **AND**
4. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time; **AND**
5. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence); **AND**
6. Baseline anti-adenovirus serotype 9 (AAV9) antibody titers $\leq 1:50$; **AND**
7. Prescribed by a neurologist with expertise in treating spinal muscular atrophy.

NOTE: To support the data requirements for an outcomes-based agreement on this drug, the prescriber is encouraged to provide ongoing clinical information upon request by Plan or Plan's authorized

representative (Evio Pharmacy Solutions).

If the member is currently receiving Nusinersen, he/she will be eligible to switch to Zolgensma, but Zolgensma and Nusinersen may not be used concomitantly.

Presymptomatic members identified through the newborn screening process are eligible for treatment pending satisfaction of other clinical requirements.

Repeat treatment or ante-partum use of Zolgensma is considered **INVESTIGATIONAL**.

Zolgensma is considered **INVESTIGATIONAL** for all other indications.

Concurrent use of Zolgensma and Nusinersen is considered **INVESTIGATIONAL**.

Additional Information

The recommended dosage of Zolgensma is 1.1×10^{14} vector genomes (vg) per kg of body weight. It should be administered as an intravenous infusion over 60 minutes. Systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg should be administered according to the FDA approved prescribing label.

FDA has issued a black-box warning for Zolgensma due to the risk of acute serious liver injury and elevated aminotransferases. Patients with pre-existing liver impairment may be at higher risk.

The FDA label states that “The safety and efficacy of Zolgensma in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.” Baseline anti-AAV9 antibody testing is performed prior to infusion using. Retesting may be performed if anti-AAV9 antibody titers are reported as >1:50.

Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time), platelet counts, and troponin-I levels should be monitored as per the prescribing label.

Where feasible, patient’s vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Zolgensma infusion.

Use of Zolgensma in premature neonates before reaching full term gestational age may not be recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

Efficacy of Zolgensma in patients with c.859G>C variant in SMN2 gene has not been evaluated.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is required .
Commercial PPO and Indemnity	Prior authorization is required .
Medicare HMO BlueSM	Prior authorization is required .
Medicare PPO BlueSM	Prior authorization is required .

Requesting Prior Authorization Using Authorization Manager

Providers will need to use [Authorization Manager](#) to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the service request is processed accurately and quickly:

- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources

- Refer to our [Authorization Manager](#) page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Zolgensma [\(085\)](#) using [Authorization Manager](#).

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to 5x10 ¹⁵ vector genomes
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Procedure Codes

ICD-10-PCS codes:	Code Description
XW033F3	Introduction of Other New Technology Therapeutic Substance into Peripheral Vein, Percutaneous Approach, New Technology Group 3

The following ICD Diagnosis Code is considered medically necessary when submitted with the codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10-CM diagnosis codes:	Code Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]

Description

Spinal Muscular Atrophy

SMA is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the *SMN1* gene located on chromosome 5. This gene produces the “survival of motor neuron” protein (SMN1), which is essential for motor neuron functioning. In 95% of cases of SMA, there is a homozygous deletion of exon 7 in the *SMN1* gene. The remaining 5% of cases are compound heterozygotes for *SMN1* exon 7 deletions and small intragenic variants.¹ Due to absent or low levels of the SMN1 protein, motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk affecting the ability to crawl, walk, sit up, and control head. In more severe cases, feeding, swallowing, and breathing are affected as well. The exact role of the SMN protein in motor neurons has not been completely elucidated, and levels of the SMN protein required for optimal functioning are unknown.²

There is wide phenotypic heterogeneity in SMA, as summarized in Table 1. This is due to the presence of *SMN2*, a modifying/backup gene, also located on chromosome 5, which is 99% identical to *SMN1*. However, 70% to 90% of the SMN2 compensatory protein produced by this gene is defective and unstable due to the lack of exon 7.³ The number of copies of the *SMN2* gene varies widely (range, 0-6), resulting in a less severe form of SMA among those with more copies of the *SMN2* gene and vice-versa.⁴ The relation between the *SMN2* copy number and SMA phenotype is summarized in Table 2. These data were generated from DNA samples of 375 patients with SMA who previously had been classified as follows: 188 with SMA type I, 110 with SMA type II, and 77 with SMA type III.⁵

Table 1. Characteristics and Subtypes of SMA

Type of SMA	Age at Symptoms Onset	Life Span	Highest Motor Milestone Achieved	SMN2 Copy Number ^a
Type 0 (antenatal-onset SMA)	Prenatal	<6 mo	Little ability to move and may be unable to breathe and swallow independently	1
Type I (infantile SMA or Werdnig-Hoffman disease)	0-6 mo	<2 y without respiratory support	Never rolls or sits unsupported	2
Type II (intermediate SMA or Dubowitz disease)	<18 mo	>2 y; »70% alive at 25 y of age	Sits independently once properly positioned; sometimes stands but never able to walk	3 or 4
Type III (Kugelberg-Welander disease)				
Subtype IIIa	>18 mo to 3 y	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well	3 or 4

Subtype IIIb	>3 y	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Walks, runs, jumps, and can participate in sports	4
Type IV (adult-onset SMA)	>21 y	Similar to that of the general population	Similar to that of the general population	4-8

Adapted from the Muscular Dystrophy Association (n.d.),⁶ National Organization for Rare Disorders (2012),⁷ Zerres et al (1995),⁸ Finkel et al (2014),⁹ and Rudnik-Schoneborn et al (2001).¹⁰

SMA: spinal muscular atrophy

^a Quantitative analysis of *SMN2* copies in 375 patients showed that 80% of SMA type I carry 1 or 2 *SMN2* copies, 82% with SMA type II carry 3 *SMN2* copies, and 96% with SMA type III carry 3 or 4 *SMN2* copies.⁵ Among 113 patients with SMA type I, 9 with 1 *SMN2* copy lived <11 months, 88 of 94 with 2 *SMN2* copies lived <21 months, and 8 of 10 with 3 *SMN2* copies lived 33 to 66 months.¹¹

Table 2. Relation Between *SMN2* Copy Numbers and SMA Phenotype

Type of SMA	Percent With 1 <i>SMN2</i> Copy	Percent With 2 <i>SMN2</i> Copies	Percent With 3 <i>SMN2</i> Copies	Percent With 4 <i>SMN2</i> Copies
Type I	6.9	73.4	19.7	0
Type II	0	10.9	81.8	7.3
Type III	0	3.9	50.6	45.5
	Probability^a of SMA Type I	Probability^a of SMA Type II		Probability^a of SMA Type III
1 <i>SMN2</i> copy	99.9	0		0
2 <i>SMN2</i> copies	97.3	2.7		0
3 <i>SMN2</i> copies	7.2	82.8		10.0
4 <i>SMN2</i> copies	1.6	14.8		83.6

Adapted from Feldkotter et al (2002).⁵

SMA: spinal muscular atrophy.

^a Probability that an unaffected child who has been tested after birth and has been found to carry a homozygous *SMN1* deletion will develop SMA type.

Diagnosis

SMA can be diagnosed using multiple molecular genetic testing techniques such as multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction or a comprehensive next-generation sequencing-based approach. Individuals are classified as having SMA if they have a homozygous deletion of the *SMN1* gene or a homozygous absence of the *SMN1* gene due to gene conversion (ie, *SMN1* gene conversion to *SMN2* gene) or a compound heterozygote variant in the *SMN1* gene. Individuals are defined as carriers if they have one copy of the *SMN1* gene on one chromosome and no copies on the other or two copies of the *SMN1* gene on one chromosome and no copies on the other. Assessing *SMN2* copy numbers as part of a diagnostic workup is important because it can provide critical information on disease progression and assist in possible clinical trial enrollment or treatment.

Because SMA symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of SMA subtypes is difficult. The incidence, as reported in the literature, is more precisely a birth prevalence rate, which is estimated between 9.1 and 10 per 100000 live births,¹² which translates to 500 new SMA cases annually.

Treatment

Medical management of SMA patients includes respiratory, nutritional, and musculoskeletal supportive care. Respiratory management includes airway clearance, antibiotic treatment of infections, noninvasive and invasive ventilation. Nutritional management includes changing food consistency, gastrostomy tube feeding, and dietician assessment. Musculoskeletal supportive care includes a variety of intervention such as equipment for mobility, teaching self-care and function, physiotherapy, spinal surgery, posture and pain management, regular exercise, and scoliosis surgery. The type and extent of supportive care can affect survival in infant-onset disease (eg, gastrostomy feeding and noninvasive/invasive ventilation).

Zolgensma™ (onasemnogene abeparvovec-xioi), a one-time gene replacement therapy is intended as an intravenous infusion for patients with SMA type I and an intrathecal infusion for SMA type II. There are four major components of this technology—the vector, the *SMN* transgene, the self-complementary DNA technology, and the promoter.¹² A brief description of each component is provided below.

- **Vector:** Nonreplicating adeno-associated virus serotype 9 that easily crosses the blood-brain barrier.
- **Transgene:** Nonintegrating copy of a stable and fully functioning human *SMN* gene that is introduced into the motor neuron cells. The gene is designed to stay in the nucleus and does not alter the patient's genome.
- **Self-complementary adeno-associated virus Inverted Terminal Repeats:** Use of self-complementary adeno-associated virus inverted terminal repeats obviates the dependence of the transgene on the patient's motor neuron-mediated synthesis of a complementary DNA strand to form the double-stranded DNA. Instead, the transgene is self-complementary, enabling rapid onset of effect.
- **Promoter:** The technology uses a chicken beta-actin hybrid promoter, which functions as a continuous promoter allowing for sustained expression of the *SMN* protein.

Because motor neurons are nondividing cells, it has been suggested that once the *SMN* gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained *SMN* protein expression with a one-time dose, and provide a durable therapeutic effect based on studies in animal models.

Summary

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the *SMN1* gene. As a consequence of absent or low levels of *SMN1* protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Zolgensma™ (onasemnogene abeparvovec-xioi) is intended as a one-time gene replacement therapy designed to deliver a functional copy of the *SMN1* gene to motor neuron cells of patients with SMA. Because motor neurons are nondividing 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.

Onasemnogene Abeparvovec-Xioi

Infantile-Onset or SMA Type I

For individuals who have SMA type I (infantile-onset) who receive Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a prospective cohort of 15 patients followed for 2 years. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. In this single phase 1 study of symptomatic infants with 2 copies of *SMN2* gene, 12 of 15 infants received the proposed therapeutic dose while 3 received the minimally effective dose. At the end of the 2-year follow-up, all 15 infants survived and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation. All 12 patients also achieved at least 1 motor milestone, with 92% of those achieving scores greater than 40 on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (a score >40 is a favorable outcome). The FDA approval was based on a pooled analysis of 21 patients from the pivotal phase I and ongoing confirmatory phase III STRIVE-US trial. The observed treatment effect on survival, event-free survival and achievement of motor functions is beyond what is typical based on the known natural history of patients with SMA type I with two copies of *SMN2*. The available published data support a clinically meaningful

durable treatment effect through 2 years. However, there is limited data to assess the long-term durability of treatment effect as well as safety related to adverse events that are rare or have delayed onset. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Presymptomatic Patients with a Diagnosis of SMA and Less Than 3 Copies of SMN2

For individuals who are presymptomatic with a genetic diagnosis of SMA and less than 3 copies of SMN2 who receive Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a prospective cohort with a planned enrollment of 44 patients and a planned follow-up of 18 to 24 months. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (SPRINT) is currently ongoing. As of March 2019, 18 patients have been treated. The median follow-up after treatment was 2.9 months (range 0.4 to 8.7). All 18 children were alive and “event free.” Among 8 patients with two copies of SMN2, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance. Data was much more limited for patients with 3 copies of SMN2. However, early increases in mean Bayley-III Gross Motor score were observed. The evidence for presymptomatic SMA patients is currently evolving.

SMA Type II

For individuals with SMA type II who receive intrathecal Zolgensma™ (onasemnogene abeparvovec-xioi), the evidence includes a single prospective cohort study with a planned enrollment of 27 patients who are up to 60 months old. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (STRONG) evaluating use of intrathecal Zolgensma™ (onasemnogene abeparvovec-xioi) administration in patients with age of symptom onset up to 60 months is currently ongoing. The data is premature but suggests some benefit as a number of patients achieved new motor milestones. The evidence is insufficient to determine the effects of technology on health outcomes.

Policy History

Date	Action
3/2024	Updated to add a note for Outcomes-based contracts.
9/2023	Policy clarified to include prior authorization requests using Authorization Manager.
8/2023	Policy revised. <ul style="list-style-type: none"> Updated number of SMN2 copies requirement from no more than 3 to 4. Effective 8/9/2023. Updated to match BCBSA updates - removed the weight requirement of ≤13.5kg at time of infusion; added new criteria requirement for baseline liver function. Policy updated for with literature review. Policy statement updated. References updated. Effective 8/9/2023.
7/2020	Clarified coding information
6/2020	BCBSA National medical policy review. References updated. Policy statements unchanged.
2/2020	New medical policy describing medically necessary and investigational indications. Effective 2/1/2020.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- [Medical Policy Terms of Use](#)
- [Managed Care Guidelines](#)
- [Indemnity/PPO Guidelines](#)
- [Clinical Exception Process](#)
- [Medical Technology Assessment Guidelines](#)

References

1. Onasemnogene abeparvovec for treating spinal muscular atrophy. Highly specialised technologies guidance. Published: 7 July 2021. Available at www.nice.org.uk/guidance/hst15. Accessed on January 31, 2023
2. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. *Am J Med Genet A*. Jul 2010;152A(7):1608-1616. PMID 20578137
3. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol*. Aug 2007;22(8):1027-1049. PMID 17761659
4. Lorson CL, Hahnen E, Androphy EJ, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci U S A*. May 25 1999;96(11):6307-6311. PMID 10339583
5. Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet*. Jul 1997;16(3):265-269. PMID 9207792
6. Feldkotter M, Schwarzer V, Wirth R, et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet*. Feb 2002;70(2):358-368. PMID 11791208
7. Muscular Dystrophy Association. Spinal Muscular Atrophy. n.d.; <https://www.mda.org/disease/spinal-muscular-atrophy>. Accessed March 12, 2020
8. National Organization for Rare Disorders, Russman B. Spinal Muscular Atrophy. 2012; <https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/>. Accessed March 12, 2020
9. Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol*. May 1995;52(5):518-523. PMID 7733848
10. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. Aug 26 2014;83(9):810-817. PMID 25080519
11. Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Borkowska J, et al. The predictive value of achieved motor milestones assessed in 441 patients with infantile spinal muscular atrophy types II and III. *Eur Neurol*. 2001;45(3):174-181. PMID 11306862
12. Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. *J Pediatr*. Jan 2013;162(1):155-159. PMID 22809660
13. Prior TW. Perspectives and diagnostic considerations in spinal muscular atrophy. *Genet Med*. Mar 2010;12(3):145-152. PMID 20057317
14. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet*. Jan 2012;20(1):27-32. PMID 21811307
15. Biogen Inc. Highlights of Prescribing Information: Spinraza (nusinersen) injection, for intrathecal use: Prescribing label. 2016; https://www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf. Accessed March 12, 2020
16. Dominguez E, Marais T, Chatauret N, et al. Intravenous scAAV9 delivery of a codon-optimized SMN1 sequence rescues SMA mice. *Hum Mol Genet*. Feb 15 2011;20(4):681-693. PMID 21118896
17. Foust KD, Nurre E, Montgomery CL, et al. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. *Nat Biotechnol*. Jan 2009;27(1):59-65. PMID 19098898
18. Foust KD, Wang X, McGovern VL, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nat Biotechnol*. Mar 2010;28(3):271-274. PMID 20190738
19. Valori CF, Ning K, Wyles M, et al. Systemic delivery of scAAV9 expressing SMN prolongs survival in a model of spinal muscular atrophy. *Sci Transl Med*. Jun 9 2010;2(35):35ra42. PMID 20538619
20. De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord*. Nov 2016;26(11):754-759. PMID 27769560
21. 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. *Neuromuscul Disord*. Mar 2010;20(3):155-161. PMID 20074952
22. Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatr Phys Ther*. Winter 2011;23(4):322-326. PMID 22090068

23. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. Dec 17 2016;388(10063):3017-3026. PMID 27939059
24. Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. *J Child Neurol*. Dec 2011;26(12):1499-1507. PMID 21940700
25. Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. *Neuromuscul Disord*. Feb 2016;26(2):126-131. PMID 26776503
26. Kaufmann P, McDermott MP, Darras BT, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology*. Oct 30 2012;79(18):1889-1897. PMID 23077013
27. 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*. Aug 1999;135(2 Pt 1):153-161. PMID 10431108
28. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. Dec 2017;82(6):883-891. PMID 29149772
29. De Vivo DC, Bertini E, Swoboda KJ et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul. Disord*. 2019 Nov;29(11). PMID 31704158
30. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. Nov 2 2017;377(18):1723-1732. PMID 29091570
31. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology*. Mar 08 2016;86(10):890-897. PMID 26865511
32. Darras BT, Chiriboga CA, Iannaccone ST et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. *Neurology*. 2019 May;92(21). PMID 31019106
33. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. Feb 15 2018;378(7):625-635. PMID 29443664
34. Biogen, RTI Health Solutions. Formulary Submission Dossier: Spinraza (Nusinersen) for Spinal Muscular Atrophy (NS-US-0199). Cambridge, MA: Biogen; 2016 December
35. Institute for Clinical and Evidence Review. Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value (Final Evidence Report April 3, 2019; Updated May 24, 2019). 2019; https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf. Accessed March 12, 2020
36. Schultz M, Swoboda KJ, Wells C, et al. AVXS-101 Gene-Replacement Therapy (GRT) Clinical Trial in Presymptomatic Spinal Muscular Atrophy (SMA): Phase 3 Study Design and Initial Baseline Demographics. The 23rd International Annual Congress of the World Muscle Society; October 2-6, 2018; Mendoza, Argentina
37. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. Nov 2 2017;377(18):1713-1722. PMID 29091557
38. Al-Zaidy SA, Kolb SJ, Lowes L et al. AVXS-101 (Onasemnogene Apeparovvec) for SMA1: Comparative Study with a Prospective Natural History Cohort. *J Neuromuscul Dis*. 2019;6(3). PMID 31381526
39. Al-Zaidy S, Pickard AS, Kotha K et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr. Pulmonol*. 2019 Feb;54(2). PMID 30548438
40. Lowes LP, Alfano LN, Arnold WD et al. Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy. *Pediatr. Neurol*. 2019 Sep;98:39-45. PMID 31277975
41. Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. *Pediatr Neurol*. Oct 2015;53(4):293-300. PMID 26260993
42. Prior TW, Krainer AR, Hua Y, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. *Am J Hum Genet*. Sep 2009;85(3):408-413. PMID 19716110
43. Inc. A. Highlights of Prescribing Information: Zolgensma (onasemnogene abeparovvec-xioi) suspension for intravenous infusion: Prescribing label. 2019; <https://www.fda.gov/media/126109/download>. Accessed March 12, 2020
44. Day JW, Feltner DE, Ogrinc F, et al. AVXS-101, Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1 (SMA1): Pivotal Study (STR1VE) Update (P.181). The 23rd International Annual Congress of the World Muscle Society; October 2-6, 2018; Mendoza, Argentina

45. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. Jun 2010;50(6):921-936. PMID 20487038
46. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache*. Oct 2011;51(9):1358-1373. PMID 21883197
47. Cure SMA. AveXis Files for FDA Approval of Gene Therapy for Spinal Muscular Atrophy Type I. 2018; <http://www.curesma.org/news/avexis-fda-approval-type-i.html>. Accessed March 12, 2020