Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Spinal Muscular Atrophy

Date of Review: June 2026

Generic Name: onasemnogene abeparvovec-brve

Date of Last Review: February 2023
Dates of Literature Search: 02/10/2022 – 03/09/2026
Brand Name (Manufacturer): Itvisma® (Novartis)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of the class update is to review new, high-quality evidence for the management of spinal muscular atrophy (SMA) published since the last Pharmacy and Therapeutics (P & T) Committee review in 2023 and to evaluate evidence for the safety and efficacy of ITVISMA (onasemnogene abeparvovec-brve), a new formulation of gene therapy for SMA.

Plain Language Summary:
- Spinal muscular atrophy (SMA) is an inherited condition which destroys nerve cells that control muscles involved in speaking, walking, breathing, and swallowing. In SMA, the muscles weaken over time and waste away. There are 4 types of SMA: Type 1 has the most severe symptoms. People with Type 2, Type 3, and Type 4 SMA may live longer lives, as their symptoms are usually less severe.
- There are 4 medicines approved in the United States to treat SMA: SPINRAZA (nusinersen), ZOLGENSMA (onasemnogene abeparvovec-xioi), ITVISMA (onasemnogene abeparvovec-brve), and EVRYSDI (risdiplam). SPINRAZA is injected into the fluid surrounding the spinal cord in the lower back every 4 months. ZOLGENSMA is administered only once as in infusion into the veins. EVRYSDI is a pill or liquid that is taken by mouth every day for life. ITVISMA is the medicine most recently approved by the FDA and is a one-time injection into the fluid surrounding the spinal cord in the lower back.
- ITVISMA was studied in children with SMA who could sit on their own but could not walk. After one year, more children who received this medicine had an improvement in their ability to move than those who did not receive any medicine (sham injection).
- Studies have shown that all 4 medicines improve most muscle function. None of the medicines help the breathing muscles, so some patients may still need a machine called a ventilator to help with breathing.
- Most of the side effects of SPINRAZA and ITVISMA were because it is injected into the fluid around the spinal cord, which can cause headache, back pain, and nausea. ZOLGENSMA and ITVISMA can damage the liver, so people who receive this medicine must have their liver monitored with regular blood tests. Side effects reported with EVRYSDI include fever, diarrhea, joint pain, mouth ulcers, and constipation.

Author: Deanna Moretz, PharmD, BCPS

- Doctors who prescribe one of these medicines must get approval from the Oregon Health Plan. This process is called prior authorization.

Research Questions:

1. What is the comparative efficacy of nusinersen (SPINRAZA), onasemnogene abeparvovec-xioi (ZOLGENSMA), and risdiplam (EVRYSDI) for treating spinal muscular atrophy (SMA)?
2. What are the comparative harms of nusinersen, onasemnogene abeparvovec-xioi and risdiplam for treating SMA?
3. What is the evidence for the safety and efficacy of ITVISMA (onasemnogene abeparvovec-brve) in treating SMA?
4. What is the efficacy and harms of co-treatment or sequential use of treatments approved by the U.S. Food and Drug Administration (FDA) to treat SMA?
5. Are there populations of patients based on specific demographic characteristics (e.g., age, race, ethnicity, socioeconomic status, co-morbidities, etc.) in which a particular treatment for SMA would be more effective or associated with less harm?

Conclusions:

- Comparative studies of the SMA disease-modifying treatments are not available as heterogeneity of study populations and outcomes make the results difficult to interpret.[1]
- No recent high-quality systematic reviews were identified. Three high-quality guidelines were recently published.[2-4]
- In 2025, Canada's Drug Agency (CDA) evaluated published evidence for the safety and efficacy of nusinersen and risdiplam for adults with SMA.[2] Based upon the available evidence, CDA does not recommend reimbursement for initiation of nusinersen in patients in patients with later-onset or more slowly progressive forms of SMA aged 18 years and older or initiation of risdiplam in patients aged older than 25 years.[2] No changes have been made to the 2021 CDA guidance for risdiplam which supports use of risdiplam to treat SMA in patients aged 2 months and older with genetic documentation of the SMA diagnosis.[5] CDA guidance (2021) recommends onasemnogene abeparvovec-xioi use in SMA patients with genetic documentation of the condition who are aged 180 days or younger.[6]
- The National Institute for Health and Care Excellence (NICE) updated guidance for onasemnogene abeparvovec-xioi in April 2023.[3] Onasemnogene abeparvovec is an option for treating SMA in people with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in infants, only if:
    - they are aged 6 months or younger, or
    - aged 7 to 12 months if treatment is agreed by the national multidisciplinary team, and
    - tracheostomy or permanent ventilation for more than 16 hours per day is not needed.[3]
- The NICE updated guidance for risdiplam in December 2023.[4] Risdiplam is recommended as an option for treating SMA in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies.[4]
- In February 2025, FDA approved a new tablet formulation of risdiplam based on pharmacokinetic studies comparing it to previously approved formulations.[7] The oral tablets are indicated for patients 2 years of age and older who weigh 20 kg or more.[7]
- In March 2026, the FDA approved a higher dosing regimen for nusinersen. The high-dose regimen starts with 50 mg loading dose every 14 days for 2 doses, followed by a 28 mg maintenance dose every 4 months starting 4 months after the last loading dose.[30] The previously approved low-dose regimen consists of a 12 mg loading dose every 14 days for 3 doses, followed by a fourth 12 mg dose 30 days after the third dose.[30] The 12 mg maintenance dose is initiated once every 4 months after completing the 4-dose loading dose regimen.[30] The manufacturer does not stipulate which dosing regimen is preferred, as the provider will determine which dosing regimen (high versus low) is optimal for their patient.

- ITVISMA (onasemnogene abeparvovec-brve) is an adeno-associated viral (AAV) vector-based gene therapy approved by FDA in November 2025 as a one-time intrathecal injection.[8] It is indicated to treat SMA in adults and pediatric patients 2 years of age and older with a confirmed mutation in the SMN1 gene.[8] The safety and efficacy of onasemnogene abeparvovec-brve is supported by data from a single, phase 3 trial (STEER).[9]
    - The STEER trial was a 52-week, phase 3, multicenter, sham-controlled, double-blind randomized controlled trial (RCT) evaluating intrathecal onasemnogene abeparvovec-brve in patients with Type 2 SMA (n=126).[9]
    - The primary efficacy endpoint was change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) score. The published minimal clinically important difference (MCID) for the HFMSE is 3 points; however, the investigators used an MCID of improvement of 1.5 points, based on another study of patients with SMA type 2 and 3.[10] MCID values documented in the literature range from 1.5 to 4 depending on the statistical method used to evaluate clinical significance. MCID values may be different for symptoms that are improving compared to symptoms that are worsening.
    - Patients treated with onasemnogene abeparvovec-brve demonstrated an average improvement of 1.88 points in HFMSE score compared with sham injection after 52 weeks (least squares mean difference [LSMD], 1.88; 95% confidence interval [CI], 0.51 to 3.25; P = 0.0074; moderate-quality evidence).[9]
    - The most frequently reported adverse events reported with onasemnogene abeparvovec-brve was upper respiratory infections, pyrexia, and upper gastrointestinal symptoms.[8] A complete summary of adverse events is presented in **Table 6**.
    - Onasemnogene abeparvovec-brve has a black boxed warning for acute serious hepatic injury and elevated aminotransferases, and monitoring liver function is recommended.[8] Patients with preexisting hepatic impairment may be at higher risk for hepatic injury.[8]
- No high-quality RCTs have assessed the efficacy and harms of co-treatment or sequential use of SMA disease-modifying treatments approved by FDA. Observational, single-arm studies and case reports have been published to evaluate sequential use of SMA treatments. These observational reports do not support changes in current PA criteria, which do not permit sequential administration of SMA therapies.
- No subgroups of patients based on demographics have been identified to show that one SMA therapy is more effective than another beyond the age ranges in the FDA-approved label for each therapy.

Recommendations:
- No PDL changes are recommended based on available evidence.
- Revise prior authorization (PA) criteria for the SMA drugs to include onasemnogene abeparvovec-brve.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The P &T Committee last reviewed FDA-approved treatments for SMA at the February 2023 meeting. The committee approved recommendations to combine PA criteria for all SMA treatments into one document called “Spinal Muscular Atrophy Drugs” as presented in **Appendix 6** with updates to clarify duration of therapy and FDA-approved age ranges.
- The PDL status for the SMA drugs is listed in **Appendix 1.** Onasemnogene abeparvovec-xioi is preferred on the PDL while the other 2 medications are non-preferred. All SMA medications require PA to ensure appropriate use of these high-cost therapies.
- From April 2024 to March 2025, 93 patients in the Oregon Health Plan (OHP) had a SMA-related diagnosis: 24 were in enrolled in the fee-for-service (FFS) program and the remaining individuals were enrolled in a coordinated care organization (CCO). In the third quarter of 2025 (July 1 to September 30) there

were 5 FFS patients with claims for nusinersen. During the same time, there were no claims for onasemnogene abeparvovec-xioi and 3 claims for risdiplam in FFS population and 13 risdiplam claims in the CCO population.

- The Health Evidence Review Commission (HERC) has addressed SMA carrier screening for pregnant women Guideline Note D17 and recommends coverage of genetic screening for SMA once in a lifetime.[11]

Background:

Spinal muscular atrophy is a rare, autosomal recessive, and progressive neuromuscular disorder caused by mutations in the SMN1 gene, which reduces levels of functional SMN protein.[12] Insufficient levels of SMN protein in motor neurons in the brainstem and spinal cord leads to malfunction, deterioration, and the eventual death of those cells.[12] Spinal muscular atrophy is characterized by progressive weakness, atrophy of skeletal muscles and hypotonia.[13] Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.[14]

The incidence of SMA is estimated at 4 to 10 in 100,000 live births.[12] Spinal muscular atrophy is the most common genetic cause of death in infants due to respiratory insufficiency.[15] The clinical phenotype and severity of SMA are influenced by the SMN2 gene, which acts as a disease modifier.[12] Higher SMN2 copy numbers provide partial compensation for SMN1 loss, with increased copy numbers associated with milder disease severity.[12] The phenotype is extremely variable. Patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[16] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. SMA Type 4 presents in adulthood (typically after age 30 years) has the mildest course and slowest progression.[12] The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[2,17]

SMA Type	Typical SMN2 copy numbers	Age of Onset	Motor Function	Median Survival	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1% of cases
1 (severe)	1-2	Birth to 6 months	Never able to sit unassisted	Less than 2 years	3.2 – 7.1 (45% of cases)
2 (intermediate)	2-3	7 - 18 months	Able to sit, but unable to independently walk	10 to 40 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
3 (mild)	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Adult	1.5 – 4.6 (30% of cases)
4 (adult)	≥ 4	Adult (2nd or 3rd decade)	Ambulatory	Adult	5% of cases

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the United States.[18] Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction.[19] Other laboratory tests can include muscle enzyme creatine kinase, electrophysiological testing such as electromyography (EMG), and nerve conduction study with repetitive

stimulation. These tests help to identify other muscle diseases, motor neuropathies, and disorders of neuromuscular junctions.[20] Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.[21] It is not possible to predict the severity of the SMA phenotype from carrier screening.[21]

Due to the difficulties in quantifying motor abilities in individuals with SMA, several functional motor scales were developed to assess functional status in people with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of children with SMA Type 1.[22] The CHOP-INTEND tool was validated in a small population of children (n=27) with SMA aged 3 to 260 months (mean age = 49 months).[23] The Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) was developed by physical therapists to assess individuals with SMA type 2 and 3.[24] The HFMSE motor assessment includes upper and lower limb activities as well as head and trunk control. Inter-rater reliability was tested on 35 children with an inter observer agreement greater than 99%.[24] The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[25] Sequential use of the HINE can identify early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[26] The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[19] The Revised Upper Limb Module (RULM) was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. It has been validated for use in SMA assessments in a variety of settings. **Table 2** provides a summary of each tool, the intended population, and scoring.

Table 2. Motor Function Exams for SMA[27]

Instrument	Domain Evaluated	Intended Population	Number of Items	Grading Scale	Score Range	MCID
6MWT	Aerobic capacity and endurance	Ambulatory patients with SMA	1 item: the distance covered by walking a flat 25-meter course over a 6-minute period	N/A	N/A	50 to 70 meters
CHOP-INTEND	Motor function	Infants with SMA Type 1	16 items scored 0 to 4	0 = no response 4 = full response	0 to 64	Unknown; clinical trials have used a change of ≥ 4 points
HFSME	Motor function	SMA Types 2 and 3	33 items scored 0 to 2	0 = no response 2 = full response	0 to 66	Change of ≥ 3 points
HINE-2	Motor milestones	All infants aged 2 months to 24 months	8 milestones with: • 3 items scored 0 to 4 • 4 items scored 0 to 3 • 2 items scores 0 to 2	0 = absence of activity Increasing points correspond to an increased level of milestone achievement	0 to 26	Unknown; however, an increase of ≥ 1 point is unlikely in infants with SMA Type 1
RULM	Upper extremity and ADL function	All individuals with SMA; commonly used to assess non-ambulatory individuals	19 items scored 0 to 2 1 unscored entry item; serves as functional class identification.	0 = unable 2 = able, no difficulty	0 to 37	Unknown, can vary: • SMA Type 2: 1.2 to 2.7 points • SMA Type 3: 3 to 6 points • Ambulatory SMA: 0.5 to 1 point • Non-ambulatory SMA: 2 to 4 points

Abbreviations: 6MWT: 6-Minute Walk Test; ADL: activities of daily living; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSME: Hammersmith Functional Motor Scale Expanded for SMA; HINE-2: Hammersmith Infant Neuromuscular Examination, Section 2; MCID: minimal clinically important difference; N/A: not applicable; RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy

Management of SMA focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Respiratory care includes the use of devices that improve ventilation, especially during sleep and viral illnesses when hypoventilation is most likely to occur, as well as methods to mechanically augment cough and clearance of respiratory secretions.[28] Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Full–time, noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition. Nutritional support includes the use of non-oral methods to deliver enteral nutrition, typically through a surgically placed feeding tube or temporary nasal tube, plus medical or surgical interventions to control gastroesophageal reflux.[28] Management of joint contractures and scoliosis involves aggressive physical therapy assessments, daily passive range of motion exercises, and use of bracing to facilitate and maintain optimal positioning of extremities and maintain the spine upright against gravity.[29]

Four treatments are approved by the FDA to treat SMA: 2 medications, nusinersen and risdiplam, and 2 gene therapies, onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve. Nusinersen was the first treatment approved for pediatric and adult patients with SMA in 2016.[30] It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.[30] Nusinersen must be administered via intrathecal injection every 4 months after the initial loading dose because ASOs do not efficiently cross the blood-brain barrier.[30] In 2020, risdiplam, an oral solution, received FDA approval to treat SMA.[31] Risdiplam is an SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[31] Risdiplam is FDA-approved for the treatment of all patients with SMA.[31] Dosing is weight-based and must be administered daily.[31]

Onasemnogene abeparvovec-xioi received FDA approval in 2019.[32] Onasemnogene abeparvovec-xioi is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[32] The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity. Onasemnogene abeparvovec-xioi is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein to enable development of motor neurons.[32] The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.[32] The fourth treatment, onasemnogene abeparvovec-brve, recently received FDA approval in November 2025. This gene therapy is similar to ZOLGENSMA but is administered via the intrathecal route as a one-time dose and is formulated in a different concentration. More details about this gene therapy are provided in the New Drug Evaluation below. **Table 3** provides a comparison of the 4 FDA-approved SMA treatments.

Table 3. FDA-Approved SMA Treatments

Drug (BRAND NAME)	**Route of Administration**	**Frequency of Administration**	**FDA-Approved Age Range**
Nusinersen (SPINRAZA)[30]	Intrathecal Injection	Loading Dose: 4 doses over 2 months Maintenance Dose: Once every 4 months	All SMA patients
Onasemnogene abeparvovec-xioi (ZOLGENSMA)[32]	Intravenous Infusion	Once	Patients less than 2 years of age with bi-allelic mutations in SMN1 gene

Onasemnogene abeparvovec-brve (ITVISMA)[8]	Intrathecal Injection	Once	Patients 2 years of age and older with confirmed mutation in SMN1 gene
Risdiplam (EVRYSDI)[7]	Oral	Once daily	All SMA patients
Abbreviations: FDA: Food and Drug Administration; SMA = spinal muscular atrophy; SMN = survival motor neuron			

The efficacy and harms of co-treatment or sequential treatment with SMA therapies is considered investigational, as no high-quality RCTs have been published to evaluate sequential or concurrent treatment.[27] Most studies are observational, single-center, and include small numbers of patients (n=4 to 37).[33-37] The lack of comparative group or randomization makes it difficult to attribute any improvement in symptoms to a given therapy when treatment is administered following gene therapy. Comparative studies of the 4 SMA disease-modifying treatments are not available. Heterogeneity of SMA treatment study results and outcomes make the results difficult to interpret.[1] In addition, there are missing data across studies on patients at follow-up, as patients who do not perform well on the intervention tend to withdraw from the study.[1] Due to the rare occurrence of SMA, the number of SMA patients enrolled in clinical trials was small and ranged from 7 to 118 people.[1] The efficacy of these treatments for children with long-term disease remains unknown, as most studies were conducted from 6 months to 5 years.[1] The long-term effects of all 4 treatments are currently unknown, because of the relatively short follow-up periods in the clinical trials.[1]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2,** which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The literature search did not identify recently published high-quality systematic reviews. After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or endpoints studied (e.g., non-clinical).[1,38-43]

New Guidelines:
High Quality Guidelines:
Canada's Drug Agency: Evidence Review for Nusinersen and Risdiplam for Adults with Spinal Muscular Atrophy (2025)
Two treatments, nusinersen and risdiplam, are publicly reimbursed in Canada, primarily for use in children.[2] The Canadian Drug Expert Committee (CDEC) reimbursement recommendations for both drugs highlighted serious limitations in the evidence for the effectiveness and safety of these treatments in adults

with SMA.[2] In particular, the evidence is limited by the lack of high-quality, comparative data, making it difficult to determine whether observed effects are due to the drugs or to other factors, and whether these effects are clinically meaningful in adults.[2]

Only one new study was found for nusinersen in adults with SMA.[2] This study compared adults treated with nusinersen with those who received no treatment over a follow-up period of up to 30 months.[2] The study had significant limitations, including a high risk of bias due to differences in patient characteristics between the treated and untreated groups (e.g., ability to sit or to walk at start of treatment), missing data, inconsistent findings within and across motor function outcomes, use of unvalidated thresholds to define clinically meaningful treatment effects, and incomplete outcome reporting.[2] These limitations make it difficult to draw reliable conclusions about the benefits or harms of nusinersen in adults with SMA.[2] No eligible comparative studies were found for risdiplam in adults aged older than 25 years with SMA.[2] No published studies were identified for nusinersen or risdiplam in adults with SMA who were previously treated with gene therapy (onasemnogene abeparvovec-xioi).[2]
Recommendation:

- CDEC does not support treatment with nusinersen in patients with later-onset or more slowly progressive forms of SMA that are aged 18 years and older or risdiplam in patients aged older than 25 years.[2]

National Institute for Health and Care Excellence: Onasemnogene Abeparvovec-xioi For Treating Spinal Muscular Atrophy
NICE guidance for onasemnogene abeparvovec-xioi in SMA was updated in 2023.[3] For infants with type 1 SMA who are 6 months or younger at the start of treatment, and who do not need permanent ventilation for more than 16 hours per day or a tracheostomy, evidence from clinical studies suggests that onasemnogene abeparvovec-xioi is effective.[3] But the studies are small and do not compare onasemnogene abeparvovec with other treatments, so it is difficult to establish how well it works.[3] Also, there is very limited evidence for infants with type 1 SMA who are older than 6 months at the start of treatment.[3] However, clinical experts advise that some infants aged between 7 and 12 months would be expected to have similar benefit to those 6 months and younger.[3] There is also a lack of long-term evidence, and no evidence in patients with more progressed type 1 SMA.[3]
Recommendations:

- Onasemnogene abeparvovec is an option for infants with clinical diagnosis of type 1 SMA with a bi-allelic mutation in the SMN1 gene, only if:
    - they are aged 6 months or younger (the primary population studied in clinical trials), or
    - aged 7 to 12 months if treatment is agreed by the national multidisciplinary team, and
    - tracheostomy or permanent ventilation for more than 16 hours per day is not needed.[3]

National Institute for Health and Care Excellence: *Risdiplam For Treating Spinal Muscular Atrophy*
NICE updated guidance for risdiplam in 2023.[4] Before the December 2023 license extension, risdiplam was only indicated for people 2 months and older with SMA.[4] Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3.[4] There is some evidence suggesting that people with type 1 SMA who have risdiplam live longer.[4] There is also some evidence suggesting risdiplam may be effective for people with pre-symptomatic SMA.[4] But there is no direct evidence comparing risdiplam with usual care for type 1 SMA.[4] And although it is likely that risdiplam has long-term benefits, there is no long-term evidence, so this is uncertain.[4]
Recommendation:

- Risdiplam is recommended as an option to treat SMA in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies.[4]

After review, 2 guidelines were excluded due to poor quality.[44,45]

New FDA Safety Alerts

Table 4. Description of New FDA Safety Alerts[46]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles
Nusinersen	SPINRAZA	5/2018	Warnings and Precautions	**Thrombocytopenia and Coagulation Abnormalities** Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. In sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) nusinersen-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients. In the sham-controlled study in patients with later-onset SMA (Study 2), two nusinersen-treated patients developed platelet counts less than 50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on day 28. Because of the risk of thrombocytopenia and coagulation abnormalities from nusinersen, patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of nusinersin and as clinically needed. **Renal Toxicity** Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Nusinersen is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of nusinersen-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of nusinersin. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

New Formulations

- In February 2025, the FDA-approved a new 5 mg tablet formulation of risdiplam.[7] Prior to this approval, risdiplam was only available as an oral powder that must be reconstituted prior to administration to provide a 0.75 mg/mL solution.[7] The oral tablets are indicated for use in patients 2 years of age and older who weigh 20 kg or more.[7] The FDA based the approval of the risdiplam tablet formulation on the 3 clinical trials that led to approval of the oral powder formulation.

- In March 2026, the FDA approved a higher dosing regimen for nusinersen. The high-dose regimen starts with 50 mg loading dose every 14 days for 2 doses, followed by a 28 mg maintenance dose every 4 months starting 4 months after the last loading dose.[30] The previously approved low-dose regimen consists of a 12 mg loading dose every 14 days for 3 doses, followed by a fourth 12 mg dose 30 days after the third dose.[30] The 12 mg maintenance dose is initiated once every 4 months after completing the 4-dose loading dose regimen.[30] The manufacturer does not stipulate which dosing regimen is preferred, as the provider will determine which dosing regimen (high versus low) is optimal for their patient. Nusinersen is FDA-approved for treatment of SMA in pediatric and adult patients.[30]

  The efficacy of the nusinersen high-dose regimen was evaluated in a multicenter, double-blind, RCT which included 75 treatment naïve patients with infantile-onset SMA (2 SMN2 copies; symptom onset before 6 months of age) randomized 2:1 to the 50/28 mg or 12/12 mg nusinersen regimen.[47] The primary efficacy endpoint was the 6-month change in Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorder (CHOP-INTEND) score in the patients receiving the high-dose regimen compared to a prespecified matched sham group from the initial study (ENDEAR) that led to approval of the low dose regimen (n=20; matched on baseline disease duration and baseline CHOP-INTEND score).[47] At day 183, the CHOP-INTEND least-squares mean total score improved (+15.1 points) in those who received 50/28 mg nusinersen and worsened (−11.1 points) in matched ENDEAR participants who received sham (difference, 26.19 (95% confidence interval = 20.7 to 31.74); statistical testing was performed using the joint-rank test where the difference in ranks was 26.06 (95% confidence interval = 17.9 to 34.2; $P < 0.0001$).[47]

  The safety of the nusinersen high-dose regimen was studied in 2 clinical trials in symptomatic patients with SMA (approximately 14 days to 65 years of age at first dose).[30] In clinical studies, 128 patients (50% male, 63% Caucasian, and 22% Asian) were treated with the high-dose regimen, including 113 exposed for at least 6 months, 95 exposed for at least 1 year, and 67 exposed for at least 2 years.[30] The most common adverse reactions in at least 10% of nusinersen-treated patients who received the high-dose regimen and occurred at least 5% more frequently than in historic matched sham-control were: pneumonia, COVID-19, pneumonia aspiration, and malnutrition in patients with infantile-onset SMA.[30]

Randomized Controlled Trials:
A total of 286 citations were manually reviewed from the initial literature search. After further review, 286 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Onasemnogene abeparvovec-brve for intrathecal injection

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:

Onasemnogene abeparvovec-brve is an AAV vector-based gene therapy intended for a one-time intrathecal injection.[8] It is indicated to treat SMA in adults and pediatric patients 2 years of age and older with confirmed mutation in the SMN1 gene.[8] Unlike onasemnogene abeparvovec-xioi, onasemnogene abeparvovec-brve is administered as a fixed dose independent of patient weight.[12] Onasemnogene abeparvovec-brve is delivered intrathecally at a lower total dose than onasemnogene abeparvovec-xioi.[12] The safety and efficacy of onasemnogene abeparvovec-brve is supported by data from the STEER trial, which is described and evaluated below in **Table 6**.

The STEER (NCT05089656) trial was a 52-week, phase 3, multicenter, sham-controlled, double-blind RCT evaluating intrathecal onasemnogene abeparvovec-brve in patients with Type 2 SMA (n =126).[9] Enrolled patients were 2 to less than 18 years of age, were treatment-naive to any other SMA therapies, and were able to sit but never walked independently.[9] The study was conducted at 29 sites in 14 countries.[9] A total of 217 patients were screened for enrollment; 4 patients did not complete the screening phase and 77 patients failed screening based on exclusion criteria, with the main reasons being scoliosis with a Cobb angle greater than 40° while sitting or severe contractures, hepatic dysfunction, and AAV9 antibody titer greater than 1:50.[9] Patients treated in the study received a course of oral corticosteroid, equivalent to oral prednisolone at 1 mg per kg of body weight per day (mg/kg/day) for a total of 30 days, starting one day prior to gene therapy administration.[12] The corticosteroid dose was tapered after the 30-day period, based on the clinical status and liver function testing.[12] Participants randomized to the sham procedure arm received placebo instead of prednisolone and followed the same administration protocol.[10] After their procedures on study day 1, participants remained at the hospital for 24−48 hours for safety monitoring.[10]

Clinical investigations of medication for SMA (including pivotal studies of both risdiplam and nusinersen) have demonstrated reduction of treatment effect size for patients with increasing age.[10] Therefore, STEER was designed to evaluate motor function changes in two age subgroups: 2 to less than 5 years of age as secondary endpoints and 5 to less than 18 years of age as exploratory endpoints.[10] A total of 71 patients were in the 2 to less than 5 years age group (42 in the onasemnogene abeparvovec-brve group and 29 in the sham group), and 55 patients in the 5 to less than 18 years age group (33 in the onasemnogene abeparvovec-brve group and 22 in the sham group).[12] In total, 126 patients received onasemnogene abeparvovec-brve (n = 75) or a sham procedure (n = 51).[9]

The primary efficacy endpoint was change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) score. The published MCID for this exam is 3 points;[27] however, the investigators used an MCID of an improvement greater than 1.5 points, as established in a 2024 study of patients with SMA types 2 and 3.[10] This study sought to determine the MCID in HFMSE score for patients with SMA type 2 and type 3 using 2 distinct methods: standard error of measurement and anchor-based using receiver operating characteristic (ROC) curve analysis.[10] These investigators identified optimal HFMSE cutoff points of −2 for type 2 and −4 for type 3 patients use the ROC analysis, whereas using the standard error, the investigators found the optimal cutoff points to be 1.5 for improvement and −3.2 for deterioration.[10] Patients treated with onasemnogene abeparvovec-brve demonstrated a statistically significant increase in HFMSE score compared with sham (LSMD 1.88; 95% CI, 0.51 to 3.25; P = 0.0074).[9]

Secondary endpoints included achievement of a least a 3-point improvement in HFMSE score at week 52 in the overall study population and in a subgroup population aged 2 to less than 5 years of age, and change from baseline in Revised Upper Limb Module (RULM) at week 52 in the overall study population and the subgroup population aged 2 to less than 5 years of age.[9] There is no established MCID for the RULM. The secondary efficacy endpoints did not reach statistical significance (see **Table 6**).[12]

Possible limitations of this study include broad inclusion of all patients regardless of baseline HFMSE and wide age range in the eligibility criteria.[9] At the time of recruitment, many younger eligible patients in certain regions had already received intravenous gene therapy, which meant the trial population was on average older than those studied in previous trials; most patients were 6 years of age or older.[10] An observation period of 12 months may also not be sufficient to permit assessment of delayed adverse events for onasemnogene abeparvovec-brve or to observe full benefit in motor function.[9]

Clinical Safety:
The safety data for onasemnogene abeparvovec-brve is derived from 2 clinical studies: one RCT conducted in 126 patients with SMA and a second open-label single-arm study conducted in 27 patients with SMA who were previously treated with nusinersen or risdiplam.[8] In the RCT, serious adverse reactions were reported in 4 patients (5%) including elevated liver enzymes (n=1), sensory disturbance (n=2), and vomiting (n=1).[8] The most frequently reported adverse events from the RCT are summarized in **Table 6**. The open-label study did not identify any additional adverse events associated with onasemnogene abeparvovec-brve administration.[8] Monitoring and data collection were not sufficient to definitively determine if sensory events observed in some participants were linked to dorsal root ganglia toxicity, a concern previously noted in primate studies.[9]

Table 6. Adverse Events Reported in Onasemnogene abeparvovec-brve-Treated Patients Compared to Sham-Treated Patients[8]

Adverse Events	**Onasemnogene abeparvovec-brve** N=75	**Sham** N=51
Upper respiratory tract infection	31 (41%)	15 (29%)
Pyrexia	19 (25%)	12 (24%)
Upper gastrointestinal symptoms	20 (27%)	8 (16%)
Hepatic enzyme increased	6 (8%)	5 (10%)
Headache	8 (11%)	2 (4%)
Dizziness	4 (5%)	1 (2%)
Pain in extremity	3 (4%)	1 (2%)
Thrombocytopenia	3 (4%)	0
Sensory disturbance	3 (3%)	1 (2%)

The manufacturer's label for onasemnogene abeparvovec-brve has a black boxed warning regarding the risk of acute serious hepatic injury and elevated aminotransferases that can occur with administration of this gene therapy.[8] Patients with preexisting hepatic impairment may be at higher risk for hepatic injury.[8] The manufacturer recommends assessing liver function by clinical examination and laboratory testing prior to intrathecal injection.[8] Administer systemic corticosteroid before and after onasemnogene abeparvovec-brve injection.[8] Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated.[8]

Look-alike / Sound-alike Error Risk Potential: Onasemnogene abeparvovec-xioi

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved motor function
2) Prolonged survival
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline to week 52 in motor function, as measured by the Hammersmith Functional Motor-Scale Expanded (HFSME).

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Proud CM, et al.[9] NCT05089656 Phase 3 MC, DB, SC, RCT Trial Duration: 52 weeks	1. OAV IT injection 1.2 x 10^{14} vector genomes x 1 dose 2. Sham IT injection x 1 dose	Demographics: -Mean age: 5.9 y -Mean age at SMA onset: 12.7 mos -Male: 49% -Race: Asian: 59% White: 11% Black: 7% American Indian: 5% Unknown: 17% - SMN2 gene copies: 2 copies: 4% 3 copies: 94% ≥ 4 copies: 2% -Baseline HFMSE score: 17.97 points (OAV) and 18.17 points (sham) Key Inclusion Criteria: -Aged 2 to 17 y with genetically confirmed SMA -Treatment-naïve -Onset of SMA symptoms ≥ 6 mos of age -Able to sit, but never walked independently Key Exclusion Criteria: -Cardiomyopathy, hepatic dysfunction, kidney disorder,	ITT: 1. 75 2. 51 PP: 1. 73 2. 50 Attrition: 1. 2 (3%) 2. 1 (2%)	Primary Endpoint: LSM change in HFMSE at 52 weeks in ITT population 1. 2.39 points 2. 0.51 points LSM difference: 1.88; 95% CI 0.51 to 3.25 P = 0.0074 Secondary Endpoints: LSM change in HFMSE at 52 weeks for patients aged ≥ 2 to <5 y 1. 3.00 2. 1.56 LSM difference: 1.44; 95% CI -0.33 to 3.22; P=0.11 Proportion with 3-point HFMSE improvement at 52 weeks in ITT group 1. n = 29 (39.2%) 2. n = 13 (26%) OR: 2.03; 95% CI 0.90 to 4.57; P = 0.088 Proportion with 3-point HFMSE improvement at 52 weeks in ≥ 2 to <5 y age group 1. n = 20 (48.8%) 2. n = 11 (37.9%) OR: 1.27; 95% CI 0.46 to 3.56; P=0.64 LSM change from baseline in RULM score at end of 52 weeks in ITT population 1. 2.44 2. 0.92	 NA NS NS NS	Any AE 1. 73 (97%) 2. 46 (90%) Serious AE 1. 21 (28%) 2. 17 (33%) Severe AE 1. 8 (11%) 2. 9 (18%) Hepatotoxicity 1. 7 (9%) 2. 5 (10%) Transient Thrombocytopenia 1. 4 (5%) 2. 2 (4%) Dorsal root ganglia toxicity 1. 2 (3%) 2. 1 (2%) p-values and CIs not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Baseline demographics balanced. Performance Bias: Low. Participants, caregivers, clinical evaluators, and study investigators were blinded. Detection Bias: Unclear. Adverse effects of active therapy may have caused unblinding. Attrition Bias: Low. Attrition rates were low. Reporting Bias: Low. Study protocol available on-line. All prespecified primary and secondary outcomes reported according to protocol. Other Bias: High. Funded by Novartis Pharma AG. Manufacturer also involved in study design, data collection, data analysis, and report writing. Several authors reported conflict of interest due to financial support from manufacturer for research or lectures. **Applicability**: Patient: Study enrolled patients with SMA type 2 aged 2 to 17 y reflects common ages treated in Medicaid population. Most patients were Asian, which may reflect the 7 Asian countries involved in the RCT.

		endocrine disorder, or severe respiratory compromise -AAV9 antibody titer > 1:50 -Active infection in past 30 days -Invasive or noninvasive ventilation in past 30 days -Surgery for scoliosis or hip fixation in past 12 mos		LSM difference: 1.52; 95% CI 0.34 to 2.71 P = 0.012 LSM change from baseline in RULM score at end of 52 weeks in ≥ 2 to <5 y age group 1. 3.27 2. 1.82 LSM difference: 1.45; 95% CI -0.22 to 3.12; P = 0.087	NA NS			Intervention: Safety and efficacy of fixed IT dose evaluated in Phase 2 trial conducted in patients aged 6 mos to < 60 mos. Comparator: Sham IT injection used as a comparator. Outcomes: Improvement in HFSME has been validated in Type 2 SMA patients. Setting: 29 sites in 14 countries including the United States, Brazil, China, Denmark, India, Malaysia, Mexico, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand and Vietnam.
Abbreviations: ARR = absolute risk reduction; AAV9 = anti-adeno-associated virus serotype 9; AE = adverse event; CI = confidence interval; DB = double blind; HFMSE = Hammersmith Functional Motor Scale-Expanded; IT = intrathecal; ITT = intention to treat; kg = kilograms; LSM = least squares mean; MC = multi-center; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OAV = onasemnogene abeparvovec-brve; OR = odds ratio: PP = per protocol; RCT = randomized clinical trial; RULM = Revised Upper Limb Module: SC = sham controlled; SAE = serious adverse event; SMA = spinal muscular atrophy; y = years.								

References:

1. Al-Taie A, Koseoglu A. Evaluation of the therapeutic efficacy and tolerability of current drug treatments on the clinical outcomes of paediatric spinal muscular atrophy type 1: A systematic review. *Paediatric Respiratory Reviews*. 48:65-71.
2. Canada's Drug Agency. Evidence Review for Spinraza (Nusinersen) and Evrysdi (Risdiplam) for Adutls with Spinal Muscular Atrophy. June 2025. https://www.cda-amc.ca/evidence-review-spinraza-nusinersen-and-evrysdi-risdiplam-adults-spinal-muscular-atrophy Accessed March 12, 2025.
3. National Institute for Health and Care Excellence. Onasemnogene abeparvovec for Treating Spinal Muscular Atrophy. Update April 2023. https://www.nice.org.uk/guidance/hst15 Accessed March 11, 2026.
4. National Institute for Health and Care Excellence. Risdiplam for Treating Spinal Muscular Atrophy. Updated December 2023. https://www.nice.org.uk/guidance/ta755 Accessed March 11, 2026.
5. CADTH Reimbursement Recommendation. Risdiplam (Evrysdi). August 2021. https://www.cda-amc.ca/sites/default/files/DRR/2021/SR0661%20Evrysdi%20Recommendation%20Final.pdf Accessed April 14, 2026.
6. CADTH Canadian Drug Expert Committee Recommendation. Onasmenogene Abeparovec (Zolgensma) March 2021. https://www.cda-amc.ca/sites/default/files/cdr/complete/SG0649%20Zolgensma%20-%20CDEC%20Final%20Recommendation%20March%2026%2C%202021%20for%20posting.pdf Accessed April 14, 2026.
7. EVRYSDI (risdiplam) Oral Solution and Oral Tablets. Prescribing Information. South San Francisco, CA. Genetech, Inc. February 2025.
8. ITVISMA (onoasemnogene abeparvovec-brve) intrathecal suspension. Prescribing Information. Bannockburn, IL; Novartis Gene Therapies, Inc. November 2025.
9. Proud CM, Vu DC, Wilmshurst JM, et al. Intrathecal onasemnogene abeparvovec in treatment-naive patients with spinal muscular atrophy: a phase 3, randomized controlled trial. *Nature Medicine*. 32(2):481-487. doi:https://dx.doi.org/10.1038/s41591-025-04103-w
10. Coratti G, Bovis F, Pera MC, et al. Determining minimal clinically important differences in the Hammersmith Functional Motor Scale Expanded for untreated spinal muscular atrophy patients: An international study. *Eur J Neurol*. Aug 2024;31(8):e16309. doi:10.1111/ene.16309
11. Health Evidence Review Commission Prioritized List. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Searchable-List.aspx Accessed March 11, 2026.

12. ITVISMA Summary Basis for Regulary Action. 11/24/2025. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/itvisma Accessed March 9, 2026.
13. Lunn MR, Wang CH. Spinal muscular atrophy. *The Lancet*. 2008/06/21/ 2008;371(9630):2120-2133. doi:https://doi.org/10.1016/S0140-6736(08)60921-6
14. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. *Annals of Neurology*. 2017;81(3):355-368. doi:10.1002/ana.24864
15. Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet (London, England)*. Jun 21 2008;371(9630):2120-33. doi:10.1016/s0140-6736(08)60921-6
16. Wirth B. An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). *Human mutation*. 2000;15(3):228-37. doi:10.1002/(sici)1098-1004(200003)15:3<228::aid-humu3>3.0.co;2-9
17. 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*. Jul 4 2017;12(1):124. doi:10.1186/s13023-017-0671-8
18. Department of Health and Human Services. Recommended Uniform Screening Panel (July 2018). 2018; https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed August 12, 2019.
19. Pechmann A, Kirschner J. Diagnosis and New Treatment Avenues in Spinal Muscular Atrophy. *Neuropediatrics*. Jun 01 2017;doi:10.1055/s-0037-1603517
20. Wang CH, Finkel RS, Bertini ES, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *J Child Neurol*. 2007;22(8):1027-1049. doi:10.1177/0883073807305788
21. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle & nerve*. Feb 2015;51(2):157-67. doi:10.1002/mus.24497
22. 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*. Mar 2010;20(3):155-61. doi:10.1016/j.nmd.2009.11.014
23. Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association*. Winter 2011;23(4):322-6. doi:10.1097/PEP.0b013e3182351f04
24. Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2003;7(4):155-9.
25. Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. *The Journal of pediatrics*. Aug 1999;135(2 Pt 1):153-61.
26. Maitre NL, Chorna O, Romeo DM, Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. *Pediatric neurology*. Dec 2016;65:31-38. doi:10.1016/j.pediatrneurol.2016.09.010
27. Kelly, R, Harrod C, Anderson R. FDA-Approved Treatments for Spinal Muscular Atrophy. Portland, OR: Center for Evidence-Based Policy, Oregon Health & Science University; June 2022.
28. Rao VK, Kapp D, Schroth M. Gene Therapy for Spinal Muscular Atrophy: An Emerging Treatment Option for a Devastating Disease. *Journal of managed care & specialty pharmacy*. Dec 2018;24(12-a Suppl):S3-s16. doi:10.18553/jmcp.2018.24.12-a.s3
29. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular disorders : NMD*. Feb 2018;28(2):103-115. doi:10.1016/j.nmd.2017.11.005
30. SPINRAZA (nusinersen) Intrathecal Injection Prescribing Information. Cambridge, MA. Biogen, Inc., March 2026.
31. EVRYSDI (risdiplam) Oral Solution Prescribing Information. South San Francisco, CA. Genetech, Inc. September 2022.
32. ZOLGENSMA (onasemnogene abeparvovec-xioi) Suspension for Intravenous Infusion Prescribing Information. Bannockburn, IL; AveXis, February 2025.

33. Proud CM, Finkel RS, Parsons JA, et al. Open-label phase IV trial evaluating nusinersen after onasemnogene abeparvovec in children with spinal muscular atrophy. *Journal of Clinical Investigation*. 2025;135(22):17.
34. Lee BH, Collins E, Lewis L, et al. Combination therapy with nusinersen and AVXS-101 in SMA type 1. Case Reports Observational Study. *Neurology*. 93(14):640-641.
35. Oechsel KF, Cartwright MS. Combination therapy with onasemnogene and risdiplam in spinal muscular atrophy type 1. Case Reports. *Muscle Nerve*. 64(4):487-490.
36. Svoboda MD, Kuntz N, Leon-Astudillo C, et al. Risdiplam treatment following onasemnogene abeparvovec in individuals with spinal muscular atrophy: a multicenter case series. Multicenter Study. *BMC Neurol*. 25(1):283.
37. Matesanz SE, Brigatti KW, Young M, Yum SW, Strauss KA. Preemptive dual therapy for children at risk for infantile-onset spinal muscular atrophy. *Ann Clin Transl Neurol*. Jul 2024;11(7):1868-1878. doi:10.1002/acn3.52093
38. McGrattan K, Walsh K, Mehl L, Kaur S, Dilly KW. Systematic literature review of the impact of spinal muscular atrophy therapies on bulbar function. *Journal of Neuromuscular Diseases*. 12(2):195-217.
39. Motta-Santos A, Noronha K, Reis C, Freitas D, Carvalho L, Andrade M. Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies. *Value in Health Regional Issues*. 42:100985.
40. O'Brien K, Nguo K, Yiu EM, Woodcock IR, Billich N, Davidson ZE. Nutrition outcomes of disease modifying therapies in spinal muscular atrophy: A systematic review. *Muscle Nerve*. 70(5):890-902.
41. Ribero VA, Daigl M, Martí Y, et al. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. *J Comp Eff Res*. Apr 2022;11(5):347-370. doi:10.2217/cer-2021-0216
42. Chongmelaxme B, Yodsurang V, Vichayachaipat P, Srimatimanon T, Sanmaneechai O. Gene-based therapy for the treatment of spinal muscular atrophy types 1 and 2 : a systematic review and meta-analysis. *Gene Therapy*. 32(4):301-330.
43. Yang D, Ruan Y, Chen Y. Safety and efficacy of gene therapy with onasemnogene abeparvovec in the treatment of spinal muscular atrophy: A systematic review and meta-analysis. *Journal of Paediatrics & Child Health*. 59(3):431-438.
44. Schroth M, Deans J, Arya K, et al. Spinal Muscular Atrophy Update in Best Practices: Recommendations for Diagnosis Considerations. *Neurol Clin Pract*. Aug 2024;14(4):e200310. doi:10.1212/cpj.0000000000200310
45. Kirschner J, Bernert G, Butoianu N, et al. 2024 update: European consensus statement on gene therapy for spinal muscular atrophy. *European Journal of Paediatric Neurology*. 51:73-78.
46. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed March 16, 2026.
47. Finkel RS, Crawford TO, Mercuri E, et al. High-dose nusinersen for spinal muscular atrophy: a phase 3 randomized trial. *Nat Med*. Mar 2026;32(3):1095-1104. doi:10.1038/s41591-025-04193-6

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL	Carveout
onasemnogene abeparvovec-xioi	ZOLGENSMA	INTRAVEN	KIT	Y	Y
onasemnogene abeparvovec-brve	ITVISMA	INTRATHEC	VIAL	N	Y
nusinersen sodium/PF	SPINRAZA	INTRATHEC	VIAL	N	
risdiplam	EVRYSDI	ORAL	SOLN RECON	N	
risdiplam	EVRYSDI	ORAL	TABLET	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to March 05, 2026>

1	exp Muscular Atrophy, Spinal/th [Therapy]	1054
2	onasemnogene abeparvovec-xioi.mp.	1
3	onasemnogene abeparvovec.mp.	344
4	Oligonucleotides, Antisense/ or nusinersen.mp.	15797
5	risdiplam.mp.	338
6	2 or 3 or 4 or 5	16058
7	1 and 6	286
8	limit 7 to (english language and humans and yr="2023 -Current" and (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review"))	

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ITVISMA safely and effectively. See full prescribing information for ITVISMA.

ITVISMA® (onasemnogene abeparvovec-brve) suspension, for intrathecal injection
Initial U.S. Approval: 2025

WARNING: SERIOUS LIVER INJURY
See full prescribing information for complete boxed warning.

- **Acute serious liver injury and elevated aminotransferases can occur with ITVISMA. (5.1)**
- **Patients with preexisting liver impairment may be at higher risk. (5.1)**
- **Prior to intrathecal injection, assess liver function by clinical examination and laboratory testing. Administer systemic corticosteroid before and after ITVISMA injection. Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated. (2.1, 2.4)**

----------INDICATIONS AND USAGE----------
ITVISMA is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with confirmed mutation in *SMN1* gene. (1)

----------DOSAGE AND ADMINISTRATION----------
For single-dose intrathecal injection only. (2)

- The recommended dose of ITVISMA is 1.2×10^{14} vector genomes (vg). (2.2)
- Administer ITVISMA as an intrathecal bolus injection over approximately 1 to 2 minutes. (2.4)
- Postpone ITVISMA in patients with infections until the infection has resolved and the patient is clinically stable. (2.1)
- Starting one day prior to ITVISMA injection, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30-day period, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose gradually over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed. Do not stop systemic corticosteroids abruptly. (2.2)
- If at any time patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a gastroenterologist or hepatologist and adjustment to the recommended corticosteroid regimen may be considered. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Each single-dose vial contains 1.2×10^{14} vg of onasemnogene abeparvovec in 3 mL of suspension. ITVISMA has a nominal concentration of 4×10^{13} vg/mL, and each vial contains an extractable volume of not less than 3 mL. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Prior to ITVISMA injection, assess liver function of patients by clinical examination and laboratory testing. Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated. (2.1, 2.4, 5.1)
- Thrombocytopenia: Monitor platelet counts before ITVISMA injection, and at least weekly for the first month and as clinically indicated until platelet counts return to baseline. (2.1, 2.4, 5.2)
- Peripheral Sensory Neuropathy: Consider complete neurologic evaluation and other testing and/or symptom management based on the patient's clinical presentation. (5.3)
- Thrombotic Microangiopathy (TMA): Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes. If clinical signs, symptoms and/or laboratory findings occur, consult a hematologist and/or nephrologist immediately to manage as clinically indicated. (5.4)
- Elevated Cardiac Troponin I: Increases in cardiac troponin I have occurred following ITVISMA injection. Consider cardiac evaluation after ITVISMA administration and consult a cardiologist as needed. (5.5)
- AAV Vector Integration and Risk of Tumorigenicity: There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Report cases of tumors in patients who received ITVISMA, to Novartis Gene Therapies, Inc. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions that occurred in at least 10% of patients were upper respiratory tract infection, upper gastrointestinal symptoms, pyrexia, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Gene Therapies at 1-833-828-3947 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Adjust patient's vaccination schedule to accommodate concomitant corticosteroid administration prior to and following ITVISMA injection. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2025

Author: Moretz

Date: June 2026

Appendix 4. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	AAV vector that uses the AAV9 capsid to deliver a functional copy of the SMN1 gene
Oral Bioavailability	N/A
Distribution and Protein Binding	Vector DNA concentrations were highest in the liver, followed by the dorsal root ganglia and spinal cord, with the lowest concentrations detected in the gonads. Vector DNA concentrations in the spinal cord tended to remain stable between 6-weeks and 12-months post-administration at all dose levels assessed. Protein binding was not reported.
Elimination	Shedding of onasemnogene abeparvovec DNA was primarily via feces. Peak shedding in participants was observed within 10-, 3-, 2-, and 8 days post-dose for stool, urine, saliva and nasal secretion, respectively. Over 90% of the vector DNA is excreted within 2 weeks after dose administration.
Half-Life	N/A
Metabolism	N/A

Abbreviations: AAV = adeno-associated virus; DNA = deoxyribonucleic acid; N/A = not applicable; SMN = survival motor gene

Appendix 5: Key Inclusion Criteria

Population	Children and adults with spinal muscular atrophy
Intervention	Nusinersen, onasemnogene abeparvovec-xioi, risdiplam, and onasemnogene abeparvovec-brve
Comparator	Placebo, sham injection, or standard of care
Outcomes	Improved motor function as assessed by exams presented in **Table 2**
Timing	1 to 5 years
Setting	Inpatient for gene therapy injections, provider office or inpatient for nusinersen injections, outpatient for risdiplam. Outcomes were followed on an outpatient basis.

Spinal Muscular Atrophy Drugs

Goal(s):

- Approve nusinersen (SPINRAZA), onasemnogene abeparvovec-xioi (ZOLGENSMA), risdiplam (EVRYSDI), or onasemnogene abeparvovec-brve (ITVISMA) for conditions supported by evidence of benefit (e.g., spinal muscular atrophy).
- ~~Incorporate 2-step review process for drugs on the high-cost drug carve-out list.~~

Length of Authorization:

- Nusinersen: Up to 8 months for initial approval and up to 12 months for renewal.
- Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve: Once in a lifetime dose.
- Risdiplam: Up to 6 months for initial approval and 12 months for renewal.

Requires PA:

- Nusinersen, onasemnogene abeparvovec-xioi, or onasemnogene abeparvovec-brve (pharmacy or provider administered claims)
- Risdiplam (pharmacy claims)

Covered Populations:

- Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve: FFS and CCO enrolled populations beginning 1/1/26
- Risdiplam and nusinersen: FFS populations only

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Dosing For Risdiplam

Age and Body Weight	Recommended Daily Dose of Risdiplam
Less than 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.2 mg/kg

Age and Body Weight	Recommended Daily Dose of Risdiplam
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code. Go to #2	
2. Is this a request for continuation of nusinersen or risdiplam therapy? Note: Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve are only approved as a single, one-time dose per lifetime	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #4 Document results of genetic testing	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the requested medication prescribed by a pediatric neurologist or a provider with experience treating SMA?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient ventilator-dependent (using at least 16 hours per day on at least 21 of the last 30 days)? Note: This assessment does not apply to patients who require ventilator assistance	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Has baseline motor assessment appropriate for age and/or intended population been assessed within the past 6 months? Examples include, but are not limited to, the following validated assessment tools: • Hammersmith Infant Neurological Examination, Section 2 (HINE-2) • Hammersmith Functional Motor Scale (HFMSE) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • The Motor Function Measure 32 items (MFM-32) • Upper Limb Module (ULM) • 6-minute walk test (6MWT)	**Yes:** Document date and assessment results Date: _____ Assessment:_____ Results:_____ Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the provider documented goals of therapy for this treatment?	**Yes:** Go to #8~~7~~	**No:** Pass to RPh. Deny; medical appropriateness.
8. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc.) or other validated pulmonary function test within the past 6 months?	**Yes:** Go to #9 Document baseline results.	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~9. Has the patient had previous administration of onasemnogene abeparvovec-xioi (ZOLGENSMA) or onasemnogene abeparvovec-brve (ITVISMA), either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the request for concomitant therapy with nusinersen and risdiplam?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
~~8.~~11. Is the request for risdiplam?	**Yes**: Go to #12	**No**: Go to #14

Approval Criteria		
~~9.~~12. Is the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
~~10.~~13. In people of child-bearing potential, is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~14.Is the request for nusinersen?	**Yes**: Go to #15	**No**: Go to #16
~~12.~~15.Is there documentation of recent safety monitoring in the past 4 months as recommended by the FDA (including platelet counts above the lower limit of normal and urinary protein concentrations < 0.2 g/L)?	**Yes:** -Approve for up to 8 months.	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the request for onasemnogene abeparvovec in an FDA-approved age? Note: onasemnogene abeparvovec-xioi (ZOLGENSMA) is approved for < 2 years of age. Onasemnogene abeparvovec-brve (ITVISMA) is approved for ≥2 years of age.	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~17.Have all the following labs been obtained: a) a baseline platelet count; b) baseline liver function tests (AST, ALT, total bilirubin, and PT); AND c.) baseline troponin-I?	**Yes:** Go to #18~~1~~	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~14.~~18.Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	**Yes:** Pass to RPh. Approval pending secondary review by DMAP. Duration: Approvals cover one lifetime dose. Approval valid for 12 months and will be extended if needed to cover treatment journey.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness
2. Has the patient received a formulation of the gene therapy onasemnogene abeparvovec?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #3

Renewal Criteria		
3. Is the patient meeting goals of therapy as documented by the provider in the initial approval?~~Has the patient shown a positive treatment response in one of the following areas?~~ ~~Documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened~~ ~~-OR-~~ ~~Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease~~ ~~-OR-~~ ~~Documentation of an improvement or lack of decline in pulmonary function compared to baseline~~	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: 6/26 (DM); 2/23 (DM); 9/19 (DM); 7/17; 3/17
Implementation: TBD; 4/1/23; 11/1/19: 9/1/17; 5/17