



Onasemnogene Apeparvovec-xioi: Gene Therapy for Spinal Muscular Atrophy

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Abstract

Objective: To review the efficacy and safety of onasemnogene abeparvovec-xioi (Zolgensma) in the treatment of spinal muscular atrophy (SMA). **Data Sources:** An English-language literature search of PubMed, MEDLINE, and Ovid (1946 to December 2019) was completed using the terms *onasemnogene*, *AVXS-101*, and *spinal muscular atrophy*. Manufacturer prescribing information, article bibliographies, and data from ClinicalTrials.gov were incorporated in the reviewed data. **Study Selection/Data Extraction:** All studies registered on ClinicalTrials.gov were incorporated in the reviewed data. **Data Synthesis:** Onasemnogene is the first agent for SMA utilizing gene therapy to directly provide survival motor neuron 1 (*SMN1*) gene to produce SMN protein. Four publications of 1 clinical trial, 1 comparison study of treatment effects, and 1 combination therapy case series have been published. **Relevance to Patient Care and Clinical Practice:** Onasemnogene is a one time dose approved by the Food and Drug Administration for SMA patients <2 years old who possess mutations in both copies of the *SMN1* gene. **Conclusion:** Onasemnogene appears to be an efficacious therapy for younger pediatric patients with SMA type 1. Concerns include drug cost and potential liver toxicity. Long-term benefits and risks have not been determined.

Keywords

onasemnogene, Zolgensma, spinal muscular atrophy, AVXS-101

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease presenting with hypotonia and muscle weakness, resulting from the progressive death of motor neurons in the spinal cord.¹ The incidence of SMA is 1 in 6000 to 10000 live births (or approximately 1-2 cases per day in the United States), and SMA is the leading genetic cause of infant deaths.^{1,2} The cause of all cases of SMA is a defect or an absence of survival motor neuron 1 (*SMN1*) gene, which produces the largest portion of SMN protein.³ *SMN1* gene is located on chromosome 5q11.2-q13.3.³ SMN protein is essential for motor neurons to continue to function.⁴ Those with SMA are still capable of producing smaller amounts of SMN protein because of the presence of multiple copies of *SMN2* genes.¹ The *SMN2* gene is only differentiated from the *SMN1* gene by a point mutation in exon 7, which causes a significant reduction in the ability to produce SMN protein.⁴ The *SMN2* gene generally produces about 10% of the necessary SMN protein.¹ Those with SMA often possess multiple copies of *SMN2*, with more copies

generally resulting in less significant disease.² SMA type 1 (SMA1) presents within the first 6 months of life and represents the largest portion of SMA cases (approximately 50%), whereas SMA4 has an adult onset (Table 1).^{1,2,5}

Before the introduction of nusinersen in 2016, the only treatment available to SMA patients was supportive in nature.¹⁰ Onasemnogene abeparvovec-xioi (onasemnogene; AVXS-101) is the first available agent for SMA utilizing gene therapy to directly provide *SMN1* gene in order to produce SMN protein.^{9,11} Onasemnogene is a one time dose approved by the Food and Drug Administration (FDA) for SMA patients less than 2 years old possessing mutations in both copies of the *SMN1* gene.¹¹ SMA1 patients with 2 to 3

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Table 1. Clinical Classification of SMA.^{5-9,a}

Type	Other Name or Description	Age of Onset	Life Expectancy	SMN2 Copy Number	Able to Sit/Stand/Walk
1 ^b	Werdnig-Hoffman disease	<6 Months	<2 Years	2	No/No/No
2	Dubowitz disease	6-18 Months	10-40 Years	3	Yes/No/No
3	Kugelberg-Welander disease or chronic juvenile	>18 Months	Adult	3-4	Yes/Yes/Assisted
4	Adult onset	>5 Years	Adult	>4	Yes/Yes/Yes

Abbreviations: SMA, spinal muscular atrophy; SMN, survival motor neuron.

^aAdapted from Claborn et al.⁵

^bPublished onasemnogene clinical trial data.

copies of *SMN2* but without symptoms are also recommended to receive therapy as soon as possible.⁴ An overview of onasemnogene is given in this article.

Data Selection

An English-language literature search of PubMed, MEDLINE, and Ovid (1946 to December 2019) was completed using the terms *onasemnogene*, *AVXS-101*, and *spinal muscular atrophy*. Three authors individually completed the literature review. Manufacturer prescribing information and article bibliographies were also appraised. All studies registered on ClinicalTrials.gov were incorporated.¹²

Pharmacology

Onasemnogene utilizes a nonreplicating adeno-associated virus 9 (AAV9) to provide a copy of the gene encoding the human SMN protein which is missing in those with SMA.¹¹ Onasemnogene is designed to have a rapid onset with continuous expression, so effects will continue long after administration.⁴ The maximum duration of effect is unknown. Prior to administration, testing for anti-AAV9 antibodies is required because titers <1:50 were necessary for inclusion in clinical trials.¹¹

Pharmacokinetics

Onasemnogene is given as a one time intravenous (IV) administration with the AAV9 capsid vector.¹³ The vector crosses the blood-brain barrier and transports the gene to the motor neuron cells in the central nervous system.^{13,14} After administration, the shed vector DNA was found in the saliva, urine, and stool.¹¹ Concentrations were undetectable at 3 weeks in the saliva and urine and by 1 to 2 months in the stool.

Clinical Trials

There are currently 4 publications of clinical trial data for onasemnogene, all reporting various results from the START study, NCT02122952 (Table 2).^{6-9,15-17} Mendell

et al⁶ report the safety results, and the other 3 publications report subgroup analyses, including motor function response, effectiveness, and health outcomes.⁷⁻⁹ Clinical outcome measures (Table 3) for motor function include the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Bayley Scales of Infant and Toddler Development gross motor subtest, and World Health Organization motor functioning criteria.¹⁸⁻²⁰ Electrophysiological testing outcomes were assessed with ulnar compound muscle action potential measurements.²¹

The START study was an open-label, phase 1, single-arm study with a historical control.⁶ Fifteen patients received a single IV infusion of onasemnogene. The first 3 patients, cohort 1, received a low dose (3.7×10^{13} vector genomes [vg]/kg), whereas cohort 2, 12 patients, received a high dose (1.1×10^{14} vg/kg).^{6,15} The doses were originally reported to be 6.7×10^{13} and 2.0×10^{14} vg/kg because of an inaccurate assay; these concentrations were retrospectively revised based on an accurate assay.¹⁵ All patients had SMA1, homozygous *SMN1* exon 7 deletions, and 2 copies of *SMN2*.⁶ Patients with the c.859G→C genetic modifier in exon 7 on *SMN2* were excluded because of the potential for a milder phenotype. One patient was excluded because of elevated anti-AAV9 antibody titers.

The primary outcome was safety, defined as any treatment-related adverse events of grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE).⁶ The secondary outcome was time until death or need for permanent ventilator assistance. A total of 56 serious adverse events were reported in 13 patients. Two of these were treatment-related CTCAE grade 4 hepatic failures based on aminotransferase levels 3 times the upper limit of normal (ULN) without other clinical manifestations. On day 30 postdosing, patient 1, cohort 1, had a serum alanine aminotransferase (ALT) level 31 times the ULN and aspartate aminotransferase (AST) level 14 times the ULN without other liver-related complications. These aminotransferase levels normalized after prednisolone treatment. The study protocol was then amended to start patients on prednisolone 1 mg/kg daily beginning 24 hours prior to treatment and continuing for 30 days or until AST/ALT

Table 2. Clinical Trials of Onasemnogene in SMA.

Study	Study Design	Patient Population	Trial Duration	Outcomes	Results
Mendell et al ⁶ , FDA ¹⁵	START study; OL ₁ phase 1, n = 15	SMA1, cohort 1 (n = 3) age 5.9-7.2 months, cohort 2 (n = 12) age 0.9- 7.9 months	Single IV infusion: cohort 1: low-dose (3.7 × 10 ¹³ vg/kg); cohort 2: high dose (1.1 × 10 ¹⁴ vg/kg) with data cutoff on August 7, 2017	Primary: Safety: treatment related serious adverse events (≥grade 3 ^a) Secondary: Time until death or need for permanent ventilation ^b	Safety <ul style="list-style-type: none"> Treatment related serious AE (grade 4^b): 2 of 56 events. <ul style="list-style-type: none"> Cohort 1, patient 1: ALT 31 times ULN, AST 14 times ULN without elevated indirect bilirubin or alkaline phosphatase, or clinical manifestations Cohort 2 patient: ALT 35 times ULN, AST 37 times ULN, resolved with additional prednisolone. Treatment related non-serious AE: 3 of 241 events. 2 patients with asymptomatic ALT/AST elevations less than 10 times ULN not requiring additional prednisolone. Death or need for permanent mechanical ventilation at data cutoff <ul style="list-style-type: none"> 0/15 Patients vs historical cohort 92% Median age: cohort 1, 30.8 months; cohort 2, 25.7 months Pulmonary <ul style="list-style-type: none"> No patient reached pulmonary end point (permanent ventilation^b) At baseline: 2/12 (17%) required NIV Final visit: 5/12 (42%) required NIV; the 3 that started during the 2-year period required it because of viral illness, and it was maintained Nutrition and swallow function <ul style="list-style-type: none"> Safely swallow thin liquids: at baseline, 4/12 (33%); final visit, 10/12 (83%) Safely swallow to allow oral feeding: at baseline, 7/12 (58%); final visit, 11/12 (92%) Exclusively fed by mouth: at baseline, 7/12 (58%); final visit, 6/12 (50%) Hospitalizations <ul style="list-style-type: none"> 10/12 (83%) Required at least 1 hospitalization Respiratory illness related: average 1.4 per year (SD = 0.41; range = 0-4.8) Mean proportion of study time hospitalized: 4.4% (range 0%-18.3%) Mean unadjusted annualized rate of hospitalizations (Total hospitalizations/ Total number of subject years followed): 2.1 (range 0-7.6) Mean LOS per hospitalization for those hospitalized: 6.7 days (range 3-12.1) Motor milestones <ul style="list-style-type: none"> Full head control: 11/12 (92%) Sitting unassisted: <ul style="list-style-type: none"> ≥ 5 s: 11/12 (92%) ≥ 10 s: 10/12 (83%) ≥ 30 s: 9/12 (75%) Roll: 9/12 (75%) Crawl, pull to stand, and walk independently: 2/12 (17%)
Al-Zaidy et al ⁸	Subgroup analysis of START cohort 2, n = 12	Cohort 2	Follow-up on days 7, 14, 21, and 30, then monthly visits through month 12 postdose, then every 3 months through 2 years postdose. Last visit was December 2017	Exploratory health- related outcomes: pulmonary interventions, nutritional requirements, swallow function, hospitalizations, and motor function	

(continued)

Table 2. (continued)

Study	Study Design	Patient Population	Trial Duration	Outcomes	Results
Lowes et al ⁷	Subgroup analysis of START cohort 2, n = 12	Group 1: early dosing/low motor, n = 3 Group 2: late dosing, n = 6 Group 3: early dosing/high motor, n = 3	Monthly visits through 24 months postdose	Exploratory: motor milestone achievement of sitting unassisted, CHOP INTEND scores	Motor milestone <ul style="list-style-type: none"> • Sitting unassisted ≥ 5 s, n (%) <ul style="list-style-type: none"> ◦ Early dosing/low motor: 3 (100) ◦ Late dosing: 5 (83) • Sitting unassisted ≥ 30 s, n (%) <ul style="list-style-type: none"> ◦ Early dosing/low motor: 3 (100) ◦ Late dosing: 3 (50) ◦ Early dosing/high motor: 3 (100) <p>CHOP-INTEND</p> <ul style="list-style-type: none"> • Mean score increase (SD) 1 month postdosing <ul style="list-style-type: none"> ◦ Early dosing/low motor: 13.7 (2.08) ◦ Late dosing: 7.3 (3.56) ◦ Early dosing/high motor: 10.7 (2.52) • Mean score increase (SD) from baseline to 24 months <ul style="list-style-type: none"> ◦ Early dosing/low motor: 35.0 (6.24) ◦ Late dosing: 23.3 (9.77) ◦ Early dosing/high motor: 16.3 (2.08) • Mean score (SD) at 24 months <ul style="list-style-type: none"> ◦ Early dosing/low motor: 50.7 (5.77) ◦ Late dosing: 49.8 (16.64) ◦ Early dosing/high motor: 60.3 (6.35)
Al-Zaidy et al ⁹	Subgroup analysis of START cohort 2, n = 12	START cohort 2 (n = 12), NNI101 natural history cohort of SMA1 infants (n = 16), and NNI101 healthy infants (n = 27)	START cohort 2, closed between December 2014 and December 2015, 24 months follow-up data set compared with NNI101 infants who completed their first visit between December 2012 and September 2014	Exploratory: event free survival, CHOP-INTEND scores, motor milestone achievements, CMAP and adverse events	Survival <ul style="list-style-type: none"> • START cohort 2: 12/12 (100%) survival (mean age of 27.8 months at last follow-up), no patient met composite (death or permanent ventilation^b at 24 months) • NNI101 SMA1: 10/16 (63%) met study composite end point (death or tracheostomy) by mean age of 9.6 months (however, of those who did not meet the end point, 5 were withdrawn from the study or lost to follow-up [mean age 10.6 months]) • Death: START cohort 2, none; NNI101 SMA1, 8 (50%) died, mean age 8.9 months <p>Motor function</p> <ul style="list-style-type: none"> • Average CHOP-INTEND score: <ul style="list-style-type: none"> ◦ 0 Months of age: NNI101 SMA1, 19; START cohort 2: 37 ◦ 12 Months of age: NNI101 SMA1, 10.1; START cohort 2: 50 ◦ 24 Months of age: NNI101 SMA1, 5.3; START cohort 2: 56.5 • Ulnar CMAP peak area (means): <ul style="list-style-type: none"> ◦ NNI101 SMA1: 0.61 mV/s at 6 months of age, 0.12 mV/s at 12 months of age, 0.02 at 24 months ◦ START cohort 2: 1.1 mV/s at 6 months of age, 2.8 mV/s at 12 months of age, 3.2 mV/s at 42 months ◦ NNI101 healthy: 11.3 mV/s at 6 months of age, 14.6 mV/s at 24 months of age

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potentials; FDA, Food and Drug Administration; IV, intravenous; LOS, length of stay; NIV, noninvasive ventilation; NNI101, NeuroNEXT (National Network for Excellence in Neuroscience Clinical Trials) SMA Infant Biomarker Study; OL, open label; SMA, spinal muscular atrophy; SMA1, SMA type 1; SMN1, spinal motor neuron; ULN, upper limit of normal; yG, vector genomes.

^aCommon Terminology Criteria for Adverse Events (CTCAE); hepatic failure defined as abnormal laboratory test levels (including aminotransferase 3 times ULN) or drug-induced liver injury defined by Hy's law. Grade 3: asterixis, mild encephalopathy, drug-induced liver injury, limiting self-care activities of daily living; Grade 4: life-threatening consequences, moderate to severe encephalopathy. ^{16,17}

^bPermanent ventilation defined as ≥ 16 h/d for at least 14 consecutive days without acute illness, perioperative use, or tracheostomy placement. ⁶⁸

Table 3. Clinical Outcome Measures in SMA Trials.¹⁸⁻²¹

Clinical Outcome Measure	Type of Assessment	Description
BSID-III	Motor function test	Five domains: cognitive, language, motor, social-emotional, and adaptive functioning. Gross motor subtest measures head control, trunk control and locomotion, and motor planning. Sits without support defined as ≥ 5 s and ≥ 30 s
CHOP-INTEND	Motor function test	Sixteen-item scale designed for SMA type I. Higher scores equal better function; maximum score is 64 points
CMAP	Electrophysiological testing	Electrophysiological testing of the ulnar nerve correlates with motor function
WHO motor functioning criteria	Motor milestone test	Six gross motor milestones: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. Sitting without support defined as sitting up straight with head erect for ≥ 10 s without using arms or hands for balance

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potentials; SMA, spinal muscular atrophy; WHO, World Health Organization.

were less than 120 IU/L, followed by a taper. The second event, a cohort 2 patient, required additional prednisolone to decrease aminotransferase levels. Three of 241 nonserious adverse events were treatment-related asymptomatic increases in serum aminotransferase levels (<10 times ULN) not requiring additional prednisolone. For the secondary outcome, all patients reached an age of 20 months (0% mortality) and did not require permanent mechanical ventilation, compared with 92% of historical control patients requiring permanent mechanical ventilation.

Al-Zaidy et al⁸ expanded on the health outcomes of the 12 patients treated in cohort 2 of the START study. These patients were followed for 24 months post-treatment dose, and the health outcomes described were pulmonary support, nutritional support and swallow function, rates of hospitalization, and motor function.⁸ No patient required permanent mechanical ventilation; however, at baseline, 2/12 (17%) required noninvasive ventilation, and at the final visit of the 24-month period, 5/12 (42%) required noninvasive ventilation.^{6,8} These patients had early symptom onset and rapid disease progression.⁸ Improvement was seen in the number of patients able to safely swallow thin liquids and for partial oral feeding (10 [83%] and 11 [92%], respectively, at the end of follow-up), whereas, compared with natural history studies of infants with SMA1 older than 12 months of age, 100% required either feeding and/or ventilator support.^{8,22} Patients in natural history studies did not achieve motor milestones, whereas 92% of infants treated with onasemnogene were able to speak, have full head control, and sit independently for ≥ 5 s at 2 years posttreatment.^{8,22} Additionally, those treated with onasemnogene had a mean annual hospitalization rate of 2.1 hospitalizations per year compared with natural history rates of 4.2 to 7.6 hospitalizations per year.

Lowes et al⁷ characterized motor function responses of the 12 cohort 2 patients. Patients were divided into 3 groups according to age at dosing (≥ 3 or ≥ 3 months) and baseline CHOP-INTEND scores (≥ 20 or ≥ 20 points).⁷ The 3 groups were early dosing/low motor, late dosing, and early dosing/high motor. In the first month postdosing, the early dosing/low motor group, with severe motor impairment, had the greatest improvement in CHOP-INTEND score (mean increase = 13.7; SD = 2.08) as compared with late dosing (mean increase = 7.3; SD = 3.56) and early dosing/high motor (mean increase = 10.7; SD = 2.52). At the 24-month follow-up, the CHOP-INTEND mean score increase was greatest in the early dosing/low motor and lowest in the early dosing/high motor group. Of note, the mean score increase was limited in the early dosing/high motor group because of higher baseline CHOP-INTEND scores and 2 of the 3 patients reaching the maximum score. These results are in comparison to a natural history cohort whose CHOP-INTEND score decreased a mean 10.7 points from age 6 to 12 months.²² Two patients in the early dosing/high motor group even achieved standing with and without assistance at the 24-month follow-up. The authors concluded that these results support the consensus expert opinion to identify and treat patients with 2 to 3 copies of *SMN2* as soon as possible in order to receive maximal benefit.^{7,23}

In another study by Al-Zaidy et al,⁹ the 12 infants in cohort 2 of the START study were compared with patients enrolled in the National Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) SMA Infant Biomarker Study (NN101) study (NCT01736553).⁹ Two cohorts from the NN101 study were used, comparing infants with a natural history of SMA1 and healthy infants. Patients with SMA1, in NN101 and START, were similar in age, symptomatic prior to 6 months of age, and had similar genetic profiles. The NN101 healthy infants were matched

for age, sex, birth weight, and height. Comparing the 2 cohorts with SMA1, onasemnogene treatment demonstrated improved outcomes 2 years posttreatment with regard to survival, motor function, and motor milestones. Event-free survival was 100% in the onasemnogene group compared with 38% in the NN101 SMA1 group. The durability of onasemnogene efficacy and favorable safety results were noted because no decline in motor function was observed. Although there have been 22 additional adverse events since the Mendell et al⁶ study was published, the adverse events were disease-related.⁹

Comparison and Combination Studies With Nusinersen

Onasemnogene represents the second novel therapy for SMA. The first was nusinersen, FDA approved in December 2016.¹⁰ Although their mechanisms of action vary significantly, they both have a common objective to increase the production of SMN protein in motor neurons. This will further escalate motor function and survival. Nusinersen is a modified antisense oligonucleotide that binds to *SMN2* to increase exon 7 incorporation into mRNA *SMN2*.¹⁰ This promotes an enhanced production of full-length, functional SMN protein. Administered intrathecally, nusinersen is given at scheduled intervals in the first 2 months, with maintenance doses every 4 months.¹⁰

To date, there are no head-to-head studies comparing onasemnogene with nusinersen. One study has been published estimating the treatment effects of onasemnogene relative to nusinersen by comparing data from 2 separate clinical trials (onasemnogene phase I, START trial vs nusinersen phase III, ENDEAR trial).^{6,14,24} Regarding overall survival, 100% of the onasemnogene versus 84% of the nusinersen patients were alive at last visit. Finkel et al²⁴ estimated that the number needed to treat to prevent 1 more death with onasemnogene over nusinersen was 7 (95% CI = 4.1-12.2), with the probability of preventing death 20% higher in the onasemnogene group (RR = 1.2; 95% CI = 1.1-1.3). The authors concluded that onasemnogene might have an efficacy advantage relative to nusinersen for various end points studied.

The results of this comparison study are presented with caution because the authors identify several study limitations and personal disclosures.¹⁴ Furthermore, 2 letters have been published in response to this article. One argued that study/patient differences invalidate various calculations presented.²⁵ This further shows the need for randomized, head-to-head clinical trials to determine estimates of comparative efficacy.

As with the comparison of onasemnogene with nusinersen, the questions of efficacy and safety with combination therapy remain unanswered. Because of the distinct differences in pharmacology, combination therapy may be of

interest. Yet neither manufacturer recommends combination therapy because clinical evidence for use is lacking. A single observational study without controls is the extent of the current data. Lee et al²⁶ describe 2 patients with SMA1, both treated with nusinersen followed by onasemnogene. Both were started on nusinersen at approximately 5 months of age, with the addition of onasemnogene around 9 months.²⁶ Combination therapy demonstrated a benefit in both cases. No adverse events related to the medications were noted. There is a great need for well-designed, prospective studies evaluating onasemnogene and nusinersen in comparison and combination in children with SMA.

Ongoing/New Trials

There are several ongoing trials of onasemnogene (Table 4).¹² NCT03421977 is a follow-up for patients in the START study for continuous safety monitoring. Another phase I trial, STRONG is investigating the safety and tolerability of onasemnogene by intrathecal administration but is currently suspended by the FDA pending further discussion regarding preclinical findings. There are 4 phase III clinical trials. STRIVE evaluated efficacy in 22 patients with SMA1 and 1 to 2 copies of *SMN2*. It was completed in November 2019, but results have not yet been published. Two additional STRIVE studies are ongoing: STRIVE-AP and STRIVE-EU. SPRINT began in April 2019 and investigates safety and efficacy in presymptomatic SMA patients. There is also a phase IV clinical trial not yet recruiting. Patients will transfer from their parent studies for long-term follow-up of safety and efficacy. Finally, the expanded access/managed access program is ongoing to allow treatment with onasemnogene for patients with SMA and 1 to 3 copies of *SMN2*.

Dosing, Administration, and Safety

The recommended dose of onasemnogene is 1.1×10^{14} vg/kg.¹¹ The medication is shipped frozen, is stored in the refrigerator, and must be thawed and used within 14 days of receipt of the medication. Administration is a single-dose IV infusion over 60 minutes. Prescribing information recommends assessing baseline liver function (physical exam, ALT, AST, bilirubin, prothrombin time), platelet counts, troponin-I, and anti-AAV9 antibody titers prior to administration. There are no known drug interactions and no dosage adjustments for renal or hepatic insufficiency. However, onasemnogene has a black box warning for acute serious liver injury, and patients with preexisting liver disease may be at higher risk. Because of the potential for liver toxicity, premedication with systemic corticosteroids equivalent to prednisolone 1 mg/kg is recommended, given 1 day prior to the infusion, and continued for at least 30 days.¹¹ Monitoring parameters include frequent aminotransferase, platelet, and

Table 4. Clinical Trials of Onasemnogene in SMA.^{4,12}

Study Type/Clinical Trial Phase	Trial Status	Location(s)	Identifier	Publication (Author/Year)	Indication
Interventional/Phase I clinical trial	Completed	United States	NCT02122952, AVXS-101-CL-101, START	Al-Zaidy et al ⁸ /2019, Al-Zaidy et al ⁹ /2019, Mendell et al ⁶ /2017, Lowes et al ⁷ /2019	SMAI
Interventional/Phase I clinical trial	Suspended	United States	NCT03381729, AVXS-101-CL-102, STRONG	—	SMA2
Interventional/Phase 3 clinical trial	Recruiting	Japan, Korea, Taiwan	NCT03837184, AVXS-101-CL-306, STRIVE-AP	—	SMAI
Interventional/Phase 3 clinical trial	Active, not recruiting	United States, Australia, Belgium, Canada, Germany, Israel, Italy, Japan, Korea, Spain, Taiwan, United Kingdom	NCT03505099, AVXS-101-CL-304, SPRINT	—	Presymptomatic SMA
Interventional/Phase 3 clinical trial	Completed	United States	NCT0306277, AVXS-101-CL-303, STRIVE	—	SMAI
Interventional/Phase 3 clinical trial	Active, not recruiting	Belgium, France, Italy, United Kingdom	NCT03461289, AVXS-101-CL-302, STRIVE-EU	—	SMAI
Observational/Clinical trial, phase not reported	Enrolling by invitation	United States	NCT03421977, START follow-up	—	SMAI
Expanded access	Available/Approved for marketing	United States	NCT03955679, AVXS-101-MAP-001	—	SMA
Interventional/Phase 4 clinical trial	Not yet recruiting	United States, Australia, Belgium, Canada, France, Italy, Japan, Korea, Spain, Taiwan, United Kingdom	NCT04042025, AVXS-101-LT-002	—	SMA I, 2, 3

Abbreviation: SMA, spinal muscular atrophy.

troponin-I levels during the first 3 months. Caregivers should be educated on proper handling and exposure to potential vector shedding in the patient's feces.¹¹

Cost and Relevance to Patient Care and Clinical Practice

Until 2016, the treatment for SMA was primarily supportive care with extensive medical costs and resources. The effect of onasemnogene on motor neuron loss has been demonstrated in the limited number of patients in clinical trials with the most severe form of SMA. To date, onasemnogene and nusinersen are the only 2 drugs approved for SMA. In 2019, the Institute for Clinical and Economic Review released a report assessing the comparative clinical efficacy and value of nusinersen and onasemnogene. They recognized that both medications can considerably improve the life of a child with SMA versus supportive care alone.²⁷ Malone et al²⁸ found a one time dose of onasemnogene as compared with lifetime treatment with nusinersen to be cost-effective. In the 2 year follow-up in clinical trials, no patient has shown deterioration of motor function, and longer studies may provide additional evidence. Additionally, the use of onasemnogene in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

Onasemnogene comes with a significant cost of the one time dose, >\$2 million.²⁹ The manufacturer, AveXis, offers a program to guide families through the steps in the treatment process. The drug company is also planning to offer an extended pay option and outcomes agreement to help with limited budget constraints of payers.²⁹ Collaborative efforts will be needed with clinicians, patients, payers, and the drug company to determine the appropriate use of onasemnogene.

Conclusion

Onasemnogene appears to be efficacious as a one time gene therapy for pediatric patients with SMA. It is currently only approved in younger patients with specific genetic mutations in *SMN1* because this was the only studied population. Medication concerns include drug cost and potential liver toxicity. Overall, onasemnogene shows promise to dramatically affect the quality of life for a patient with SMA. However, long-term benefits and risks with onasemnogene have not been determined.

Declaration of Conflicting Interests

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