

CLINICAL COMMUNICATIONS

Vice President

Angelia Szwed, MS

Director, Scientific Services

Patty Taddei-Allen, PharmD, MBA

Director, Publications

Danielle Mroz, MA

Scientific Director

Daniel Winslow, PharmD

Associate Scientific Directors

Erin Potter, PharmD
Nicholas Nowotarski, MD

Senior Clinical Content Manager

Ida Delmendo

Medical Writers

Dorothy Cooperson
Vieweg
Erin Garrow, PhD
Roshan Kalola, MD
Amanda Meyer, MS

Medical & Scientific Quality Review Editor

Jabir Bhuiyan, MS

Associate Editors

Amanda Thomas
Matthew Wynn

Assistant Editor

Thom LaPorte, MA

COPY & PRODUCTION

Vice President, Copy

Jennifer Potash

Copy Chief

Paul Silverman

Copy Supervisors

Angie DeRosa
Nicole Canfora Lupo

Senior Copy Editors

Cheney Baltz
Marie-Louise Best
Kelly King

Copy Editor

Kim Nir

Creative Director, Publishing

Melissa Feinen

Art Director

Julianne Costello

SALES & MARKETING

Vice President

Gil Hernandez

Associate Director, Business Development

Ben Baruch

Senior National Account Managers

Robert Foti
Kevin George

National Account Manager

Shaye Zyskowski

National Account Associates

Michael Bachalis
Alessandra Santorelli

OPERATIONS & FINANCE

Circulation Director

Jon Severn
circulation@mjhassoc.com

Vice President, Finance

Leah Babitz, CPA

Controller

Katherine Wyckoff

CORPORATE

President & CEO

Mike Hennessy Jr

Chief Financial Officer

Neil Glasser, CPA/CFE

Chief Marketing Officer

Brett Melillo

Chief Data Officer

Terric Townsend

Executive Vice President, Global Medical Affairs & Corporate Development

Joe Petroziello

Senior Vice President, Content

Silas Inman

Senior Vice President, Human Resources & Administration

Shari Lundenberg

Senior Vice President, Mergers & Acquisitions, Strategic Innovation

Phil Talamo

Executive Creative Director

Jeff Brown

FOUNDER

Mike Hennessy Sr
1960-2021

© 2024 Clinical Care Targeted Communications Group, LLC

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Clinical Care Targeted Communications Group, LLC, the editorial staff, or any member of the editorial advisory board. Clinical Care Targeted Communications Group, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Clinical Care Targeted Communications Group, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

This publication is sponsored by Novartis Gene Therapies, Inc.

Treatment of Spinal Muscular Atrophy: Managed Care Considerations for Gene Therapy

KEY TAKEAWAYS:

- Spinal muscular atrophy (SMA) is a genetic disease caused by mutations in the *survival motor neuron 1 (SMN1)* gene, which result in motor neuron loss and progressive muscle atrophy.¹
- Gene therapy can address the root cause of disease and stop disease progression.²
- Early treatment intervention can halt irreversible motor neuron loss, stop disease progression, and improve motor function.^{3,4}
- One-time-only infusion of ZOLGENSMA[®] (onasemnogene abeparvovec-xioi), the first and only gene therapy for SMA, is designed to halt the loss of motor neurons. ZOLGENSMA is the only therapy to address the root cause of SMA by delivering a copy of the gene encoding the survival motor neuron (SMN) protein with a one-time dose.⁵
- Treatment with ZOLGENSMA resulted in improved survival, motor milestone achievements, and independence from nutritional and respiratory support when compared with the natural history of untreated SMA.^{6,7}
- ZOLGENSMA has been studied in patients with SMA before and after symptom onset, in clinical trials and continuing long-term, follow-up studies, and Novartis Gene Therapies is evaluating real-world evidence on the effectiveness and safety of ZOLGENSMA.^{3,6-8}

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare neurodegenerative disorder.⁹ Without treatment, the most severe forms of SMA are a leading genetic cause of infant death.¹ Degradation and progressive loss of motor neurons can start before or shortly after birth in patients with SMA. Early presymptomatic treatment for SMA is critical because motor neuron loss is irreversible.^{3,4,10} Treatments for SMA have altered the disease course when compared to natural history, and previous classifications based

Indication

ZOLGENSMA is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with biallelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Limitations of Use

The safety and effectiveness of repeat administration or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information

BOXED WARNING: Serious Liver Injury and Acute Liver Failure

Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury, acute liver failure, and elevated aminotransferases can also occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing. Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated. If acute serious liver injury or acute liver failure is suspected, promptly consult a pediatric gastroenterologist or hepatologist.

Please see additional Important Safety Information throughout and accompanying [Full Prescribing Information](#).

on traditional motor milestones—such as whether a patient can sit or walk independently—have changed.¹ The clinical course of SMA has been significantly changed by disease-modifying treatments such as gene therapy. Gene therapy delivers a correct version of or modifies a defective gene, and provides treatment for genetic diseases, including SMA.^{1,11}

BACKGROUND

SMA is characterized by the degeneration of motor neurons leading to progressive muscle weakness.¹² SMA is caused by mutations in the *survival motor neuron 1 (SMN1)* gene. The *SMN1* gene is present in a region that also contains the *survival motor neuron 2 (SMN2)* gene, a homologous backup gene of *SMN1*. The 5-nucleotide difference between *SMN1* and *SMN2* affects splicing, resulting in reduced expression of full-length functional protein from the *SMN2* gene. The homozygous absence of *SMN1*, because of deletion or gene conversion, causes 95% of cases of SMA.¹² The incidence of SMA is approximately 1 in 11,000 live births worldwide. In the United States, 1 in 54 people are carriers. Because the disease follows autosomal recessive inheritance, there is a 25% chance that children of parents who are both carriers will have SMA.¹²⁻¹⁴ This historical description of SMA types is based on the age of symptom onset and highest physical milestone achieved (**Table 1**).^{15,16} There is generally an inverse correlation between the severity of SMA and number of copies of the *SMN2* gene. Having more copies of *SMN2* is associated with less severe SMA. As disease-modifying therapies for SMA have emerged, the historical classification of SMA may not adequately describe the new generation of infants with SMA who are treated early, sometimes even before onset of symptoms.¹⁵

Table 1. Classification of SMA¹⁶

| Type | Motor milestones | Typical age at onset |
|------|---------------------------------------------------------------------------|-----------------------|
| 1 | Nonsitters, cannot sit or roll | < 2 to 6 mo |
| 2 | Sitters, cannot walk independently | 6 to 18 mo |
| 3 | Can walk unassisted; may lose walking ability and become wheelchair-bound | > 18 mo |
| 4 | Mild motor impairment | Adult onset (20-30 y) |

mo, month(s); SMA, spinal muscular atrophy; y, year(s).

An analysis of 625 unrelated Spanish patients was conducted to evaluate the association between the *SMN2* copy numbers and SMA type. Data from published studies including 2834 patients worldwide were also compiled to assemble a combined cohort of 3459 patients. The analysis confirmed that a strong inverse correlation exists between the *SMN2* copy number and disease severity. However, some patients with a larger copy number were classified as having a more severe phenotype of SMA worldwide. The majority of outliers in this analysis were patients with 4 copies of *SMN2*. In the combined cohort, 96% of patients with 1 *SMN2* copy developed SMA type 1. In patients with 2 *SMN2* copies, 79% developed type 1, 16% developed type 2, and 5% developed type 3. In patients with 3 *SMN2* copies, 54% developed SMA type 2, 31% developed type 3, and 15% developed type 1. In patients with 4 *SMN2* copies, 88% developed SMA type 3, 11% developed SMA type 2, and 1% developed SMA type 1. In patients with 5 *SMN2* copies, 80% developed SMA type 3, 15% developed SMA type 2, and 5% developed SMA type 1.¹⁶

SMA type 1, which accounts for 60% of total SMA cases, is a leading cause of infant mortality when left untreated, with most patients dying before the age of 2 years.¹⁷ Most patients with untreated SMA type 1 experience respiratory failure early in life (eg, before 2 years of age) and require ventilatory support.^{17,18} Gastrointestinal complications including prolonged feeding time, quickly tiring during eating, and difficulty swallowing can also occur, for which feeding and/or nutritional support is required to avoid malnutrition.¹⁸ Patients with SMA experience muscle weakness that causes various musculoskeletal issues; physiotherapy may be prescribed for these patients. Spinal fusion and bracing may also be necessary to prevent respiratory restriction due to scoliosis.

The implementation of newborn screening has led to several important findings, including the ability to better estimate the incidence of SMA and the opportunity to initiate treatment before symptom onset.¹⁴ In the United States, newborn screening programs for SMA have been implemented in 48 states, resulting in 99% of newborn babies in the United States being screened for SMA.¹⁹ In the absence of newborn screening, SMA type 1 is diagnosed at an average of 6.3 months of age, which is months after symptom onset at an average of 2.5 months of age.⁹ Newborn screening for SMA is typically performed within 24 to 48 hours after birth^{19,20}; this affords the opportunity for earlier detection of SMA before patients become symptomatic.^{14,21} Symptoms may not appear until later in life for patients with other SMA types, such as type 3 (> 18 months) and

WARNINGS AND PRECAUTIONS

Systemic Immune Response

Patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response. Administer ZOLGENSMA to patients who are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

type 4 (≥20 years).¹⁶ Newborn screening can lead to early diagnosis and treatment, which can stop further loss of motor neurons.^{22,23} Based on the screening results, the diagnosis can be confirmed and treatment can be administered soon after birth to improve outcomes.¹⁹

HEALTH-RELATED VALUE OF EARLY TREATMENT

Early, effective therapy is needed because of the irreversible nature, rapid disease progression, and potential delays in diagnosis of SMA. Loss of motor neurons starts before or shortly after birth and is irreversible.^{10,24,25} Infantile forms of the disease progress quickly.^{25,26} The impact of SMA treatment is enhanced by treating presymptomatically when more motor neurons are still viable, compared with treatment after symptom onset.^{22,27} Delays in diagnosis may decrease the opportunity for early treatment intervention.⁹ The SMA Newborn Screening Multidisciplinary Working Group convened by Cure SMA, composed of 15 SMA experts, recommends immediate treatment for SMA in individuals with 2 to 4 copies of *SMN2* who have been diagnosed with SMA via newborn screening. Previously, this Working Group recommended watchful waiting for patients with 4 copies but revised the recommendation, reflecting the importance

of immediate treatment.^{23,28} Early treatment intervention can halt irreversible motor neuron loss, stop disease progression, and improve motor function.^{7,10,29,30}

ECONOMIC BURDEN OF SMA

SMA type 1, in particular, is associated with a considerable economic burden.³¹ The Kids' Inpatient Database (KID) is the largest all-payer pediatric inpatient care database in the United States.³² The burden of SMA type 1 was retrospectively evaluated using 2012 KID data by analyzing 3 patient groups: those with SMA type 1, those with no complex chronic conditions (CCCs), and those with other CCCs. Health care resource utilization in hospitalizations for each group were compared.³¹ Results showed that SMA was associated with higher mean total charges billed per admission, mean daily charges, and mean total cost than those in patients with no CCCs and were not statistically significantly different from those in patients with other CCCs (Table 2).³¹ Hospitalizations for patients with SMA type 1 were 4.4-fold longer than for those without CCCs, averaging 15.1 days vs 3.4 days. Similarly, the mean length of stay for hospitalizations for patients with SMA type 1 was longer than that for patients with other CCCs (11.8 days).³¹ Aside from high direct annual costs, patients

Table 2. Length of Hospital Stays and Associated Inpatient Costs (2012 Data) for Patients With SMA Type 1, Other CCCs, and No CCCs³¹

| | SMA type 1 (n = 237) | No CCC (n = 632,467) | Other CCC (n = 224,953) | SMA type 1 vs no CCC | SMA type 1 vs other CCC |
|------------------------------------------|------------------------------------|---------------------------------|------------------------------------|-------------------------|----------------------------|
| Mean length of stay, d (95% CI) | 15.1 (10.9-19.2) | 3.4 (3.3-3.5) | 11.8 (11.3-12.2) | <i>P</i> < .0001 | <i>P</i> = .1116 |
| Mean total charges (95% CI) ^a | \$150,921 (\$108,944-\$192,899) | \$19,261 (\$18,302-\$20,219) | \$112,453 (\$104,615-\$120,292) | <i>P</i> < .0001 | <i>P</i> = .0654 |
| Mean total charges/d (95% CI) | \$11,143 (\$9175-\$13,110) | \$5990 (\$5707-\$6272) | \$10,359 (\$9679-\$11,039) | <i>P</i> < .0001 | <i>P</i> = .3497 |
| Mean total costs (95% CI) ^b | \$50,190 (\$35,007-\$65,373) | \$5862 (\$5514-\$6210) | \$36,605 (\$34,187-\$39,023) | <i>P</i> < .0001 | <i>P</i> = .0724 |

CCC, complex chronic condition; d, day; SMA, spinal muscular atrophy.

^aTotal charges represent the value billed by the hospital for admission throughout the hospital stay and exclude professional fees.

^bTotal costs represent the amount paid to providers for services, which differ by payer.

Adapted from Cardenas J, Menier M, Heitzer MD, Sproule DM. High healthcare resource use in hospitalized patients with a diagnosis of spinal muscular atrophy type 1 (SMA1): retrospective analysis of the Kids' Inpatient Database (KID). *Pharmacoecon Open*. 2019;3(2):205-213. doi:10.1007/s41669-018-0093-0

WARNINGS AND PRECAUTIONS (CONTINUED)

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Table 3. Health-Related Quality of Life Scores of Patients With Spinal Muscular Atrophy³³

| Functional status | SMA type 1 | SMA type 2 | SMA type 3 |
|---------------------------|---------------|---------------|---------------|
| Permanent ventilation (n) | 18 | 9 | 0 |
| Mean HUI3 score (SD) | -0.05 (0.10) | 0.10 (0.11) | — |
| Range | -0.20 to 0.13 | -0.02 to 0.31 | — |
| Nonsitters (n) | 5 | 51 | 9 |
| Mean HUI3 score (SD) | 0.06 (0.10) | 0.12 (0.12) | 0.14 (0.13) |
| Range | -0.03 to 0.21 | -0.16 to 0.41 | -0.10 to 0.34 |
| Sitters (n) | 4 | 81 | 41 |
| Mean HUI3 score (SD) | 0.11 (0.21) | 0.26 (0.16) | 0.23 (0.11) |
| Range | -0.14 to 0.35 | -0.20 to 0.70 | 0.04 to 0.48 |
| Walk with support (n) | 0 | 6 | 13 |
| Mean HUI3 score (SD) | — | 0.44 (0.12) | 0.35 (0.21) |
| Range | — | 0.32 to 0.59 | 0.02 to 0.63 |
| Walk independently (n) | 0 | 3 | 42 |
| Mean HUI3 score (SD) | — | 0.58 (0.15) | 0.64 (0.24) |
| Range | — | 0.48 to 0.76 | -0.04 to 1 |
| Attribute scores | SMA type 1 | SMA type 2 | SMA type 3 |
| Ambulation (n) | 31 | 171 | 122 |
| Mean score (SD) | 0.01 (0.06) | 0.04 (0.14) | 0.32 (0.36) |
| Range | 0.00 to 0.36 | 0 to 1 | 0 to 1 |
| Dexterity (n) | 31 | 168 | 120 |
| Mean score (SD) | 0.13 (0.27) | 0.57 (0.35) | 0.78 (0.27) |
| Range | 0 to 1 | 0 to 1 | 0 to 1 |

HUI3, Health Utilities Index Mark 3; SMA, spinal muscular atrophy.

HUI3 scores can range from -0.36 (worst health state) to 0.00 (death) to 1.00 (perfect health).³³

with SMA incur additional costs, such as those associated with appointments, time, financial costs related to condition management, and psychosocial costs. Patients with SMA type 1 experienced an average of 4.2 hospitalizations per year, signifying that the annual charges for these patients may be much higher than previous studies suggest.³¹

QUALITY OF LIFE BURDEN OF SMA

The results of an analysis by Belter and colleagues showed that patients with more severe SMA had lower health-related quality of life (HRQOL) utility scores as compared with patients with less severe types of SMA. Survey data were collected from 194 males and 284 females registered in the Cure SMA database, which included 121 patients with SMA type 1 (25%), 225 patients with SMA type 2 (47%), and 132 patients with SMA type 3 (28%). Most of the surveys were completed by a parent or caregiver. The mean (SD) age at the time of the survey was 17.1 (16.8) years (SMA type 1, 4.1 [5.9] years; SMA type 2, 17.2 [14.3] years; SMA type 3, 28.6 [18.8] years).³³

The Health Utilities Index Mark 3 (HUI3) system assessing 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) was used to calculate HRQOL values, with lower scores indicating a worse health state. Scores can range from -0.36 (worst health state) through 0.00 (death) to 1.00 (perfect health). Among patients who required permanent ventilation, HUI3 scores were lower for patients with SMA type 1 than for those with SMA type 2 (Table 3). Patients who could walk had higher HUI3 scores than did those who could only sit; scores were also higher for patients with SMA type 3 than for those with SMA type 1.³³

Further results from the same study showed that ambulation and dexterity scores were lower in patients with SMA type 1 than in patients with SMA type 2. One limitation of this study was that some of the attributes evaluated (eg, vision, hearing) are not related to SMA. In addition, the HUI3 is not useful for evaluating changes over time in patients who never achieve motor milestones.³³

HUMANISTIC BURDEN OF SMA

Caregivers and patients with SMA both experience burdens related to the disease. A total of 965 patients and 962 caregivers identified from membership lists in the Cure SMA Canada and Muscular Dystrophy Canada databases were surveyed to evaluate the disease burden. Ninety-five employed patient survey participants reported

WARNINGS AND PRECAUTIONS (CONTINUED)

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported to occur generally within the first two weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor platelet counts closely as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

an annual median of 9 sick days due to SMA. Among the 100 patients who reported changes in work responsibilities, 49% reported reduced working hours and 34% reported the need to take unpaid leave.³⁴

According to caregivers, a patient with SMA received unpaid care from a median of 2 other individuals; approximately 35 hours per week were devoted to caring for the patient. Furthermore, 46.5% of caregivers reported that a paid professional caregiver provided support to the person with SMA. Additionally, 19.3% of caregivers (183/948) reported increased care for the patient with SMA outside of work hours, 39.9% (378/948) reported reduced working hours, and 18.6% (176/948) reported taking extra unpaid leave or quitting their job entirely.³⁴

Parents of children with SMA and patients with this disease have also reported experiencing loss of sleep, increased stress, social stigma, limitations on social activities, pressure on family finances, emotional difficulties, and the feeling of being consumed by caregiving.³⁵

CURRENTLY AVAILABLE TREATMENTS

There are currently 3 US Food and Drug Administration (FDA)-approved treatments available for SMA: SPINRAZA (nusinersen injection, for intrathecal use; Biogen), EVRYSDI (risdiplam for oral solution; Genentech, Inc.), and ZOLGENSMA® (onasemnogene abeparovex-xioi suspension, for intravenous infusion; Novartis Gene Therapies, Inc.).^{5,36-38} Nusinersen and risdiplam require chronic administration, whereas ZOLGENSMA is a one-time gene therapy. Although all 3 treatments address the cause of SMA by increasing the levels of SMN protein, their mechanisms of actions differ.^{5,14,21,36,37} These mechanisms are briefly discussed below. There are no head-to-head clinical studies comparing the safety and efficacy of the treatments for SMA.

Nusinersen and Risdiplam

Nusinersen, approved by the FDA in 2016, is indicated for the treatment of SMA in pediatric and adult patients. The treatment is administered chronically and is for intrathecal administration only. Patients receive 4 loading doses, with the first 3 doses given at 14-day intervals; the fourth loading dose is given at 30 days after the third dose, followed by administration of a maintenance dose every 4 months thereafter. This SMN2-directed antisense oligonucleotide enhances exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts, leading to increased production of full-length SMN protein.³⁶

Risdiplam, FDA-approved in 2020 and indicated for the treatment of SMA in pediatric and adult patients, is administered orally on a daily basis. This small-molecule treatment enhances the splicing of SMN2 and leads to the retention of exon 7 in mRNA and subsequent production of full-length SMN protein.³⁷

ABOUT GENE THERAPY AND ZOLGENSMA

ZOLGENSMA, FDA-approved in 2019, is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients younger than 2 years of age with SMA with biallelic mutations in the *SMN1* gene. The safety and effectiveness of repeat administration or the use in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA. ZOLGENSMA is a one-time infusion and is designed to halt the loss of motor neurons through continuous expression of functional SMN protein via introduction of an SMN transgene.⁵ Prior to infusion, testing for the presence of anti-AAV9 antibodies is required. The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Retesting may be performed if anti-AAV9 antibody titers are reported as positive or elevated.⁵

Gene therapy involves the transfer of genetic material to address the cause of the disease.^{2,39} AAV is often used as a vector for gene delivery, including for ZOLGENSMA. ZOLGENSMA is a nonreplicating, recombinant adeno-associated virus 9 (AAV9) containing a transgene encoding the human SMN protein. This virus is not known to cause disease in humans. The SMN transgene is designed to be maintained as an episome in the nuclei of transduced cells.⁴⁰ ZOLGENSMA addresses the root cause of the disease by providing a functional SMN gene, continuously delivering SMN protein.⁵

DEMONSTRATED EFFICACY OF ZOLGENSMA: CLINICAL DATA OVERVIEW

Several clinical studies—STRIVE (NCT03306277), SPRINT (NCT03505099), START (NCT02122952) (Table 4), and the ongoing Long-Term Follow-Up (LTFU) studies for START (LTFU; NCT03421977) and STRIVE and SPRINT (NCT04042025) (Table 5)—have evaluated the efficacy and safety of ZOLGENSMA in patients with SMA.^{3-8,41-47,49} In the STRIVE open-label, single arm, single-dose, multicenter, phase 3 trial, ZOLGENSMA was evaluated for its efficacy and safety

WARNINGS AND PRECAUTIONS (CONTINUED)

Elevated Troponin-I

Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards. Consider consultation with a cardiologist if troponin elevations are accompanied by clinical signs or symptoms.

in symptomatic infants younger than 6 months with SMA type 1.⁶ Results from STRIVE showed that 91% (20/22)* of patients were alive and free of permanent ventilation at the 14-months-of-age study visit, which was a primary end point; these results were maintained through 18 months of age. The majority of patients (59%; 13/22) achieved sitting without support for at least 30 seconds at the 18-months-of-age study visit, a primary end point.⁶

SPRINT, a phase 3, multicenter, single-arm study, evaluated the efficacy and safety of ZOLGENSMA for presymptomatic children treated at up to 6 weeks of life.^{3,4} SPRINT enrolled infants with a

genetic diagnosis of SMA, 2 or 3 copies of *SMN2*, and no clinical evidence of neuromuscular disease.^{3,4} The results showed that 100% (29/29) of patients demonstrated event-free survival and were free of permanent ventilation or ventilatory support of any kind.^{3,8} Of the patients with 2 copies of *SMN2*, 100% (14/14) achieved the primary end point of sitting independently for at least 30 seconds at the study end (as per the Bayley Scale of Infant and Toddler Development [BSID]), with 79% (11/14) achieving the milestone within the normal World Health Organization (WHO) developmental window, and 93% (13/14) able to maintain weight at or above the third

*One patient was initially classified as presymptomatic and removed from the intent-to-treat (ITT) data set included in the Prescribing Information. The patient has been confirmed to be symptomatic at baseline and included in the final ITT analysis.⁴⁸

Table 4. Clinical Studies of ZOLGENSMA® (onasemnogene abeparvovec-xioi)^{3-8,41-47,a}

| | STRIVE-US (NCT03306277) | SPRINT (NCT03505099) | START (NCT02122952) |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design | Phase 3, open-label, single-dose, multicenter, single-arm | Phase 3, open-label, single-dose, multicenter | Phase 1, open-label, dose-escalation |
| Patient population | <ul style="list-style-type: none"> • 22 patients^b | <ul style="list-style-type: none"> • 14 patients with 2 copies of <i>SMN2</i> • 15 patients with 3 copies of <i>SMN2</i> | <ul style="list-style-type: none"> • 3 patients given a low dose^c • 12 patients given a high dose^c |
| Patient characteristics | <ul style="list-style-type: none"> • Symptomatic patients with SMA type 1 • Age < 6 mo at dosing • Biallelic <i>SMN1</i> mutations • 1 or 2 copies of <i>SMN2</i> • Anti-AAV9 antibody titer ≤ 1:50 | <ul style="list-style-type: none"> • Presymptomatic SMA • Age ≤ 6 wk • Biallelic <i>SMN1</i> mutations • 2 or 3 copies of <i>SMN2</i> • Anti-AAV9 antibody titer ≤ 1:50 • Compound muscle action potential ≥ 2 mV at baseline | <ul style="list-style-type: none"> • Symptomatic patients with SMA type 1 • Age ≤ 9 mo (first 9 patients), age ≤ 6 mo (last 6 patients) • Biallelic <i>SMN1</i> mutations • 2 copies of <i>SMN2</i> |
| Primary end point(s) | <ul style="list-style-type: none"> • Functional independent sitting for ≥ 30 s at age 18 mo (BSID-III item 26) • Event-free survival at 14 mo^d | <ul style="list-style-type: none"> • Functional, independent sitting for ≥ 30 s up to age 18 mo (2 copies of <i>SMN2</i>) • Ability to stand without support for ≥ 3 s at any visit up to age 24 mo (3 copies of <i>SMN2</i>) | <ul style="list-style-type: none"> • Safety |
| Length of study | <ul style="list-style-type: none"> • Until age 18 mo | <ul style="list-style-type: none"> • Until age 18 mo (2 copies of <i>SMN2</i>) • Until age 24 mo (3 copies of <i>SMN2</i>) | <ul style="list-style-type: none"> • 24 mo |

Continued

WARNINGS AND PRECAUTIONS (CONTINUED)

AAV Vector Integration and Risk of Tumorigenicity

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Cases of tumor have been reported in patients who received ZOLGENSMA post-approval; information on the cases is limited and causal relationship cannot be established. Report cases of tumor development in patients who received ZOLGENSMA to Novartis Gene Therapies, Inc. at 1-833-828-3947.

percentile without need for nonoral or mechanical feeding support.³ Of the patients with 3 copies of *SMN2*, 100% (15/15) achieved the primary end point of standing alone for at least 3 seconds (BSID), with 93% (14/15) achieving this milestone within the normal WHO developmental window.⁸

START, a 2-year, open-label, phase 1 study, evaluated the efficacy and safety of ZOLGENSMA in patients with SMA type 1.^{7,41} Symptomatic patients showing clinical signs of SMA before 6 months of age were divided into 2 cohorts: a low-dose cohort (n = 3) and a high-dose cohort (n = 12). The dosage received by patients in the low-dose cohort was approximately one-third of that received by patients in the high-dose cohort. The high dose was selected as the therapeutic dose, and it subsequently became the approved dose. However, the precise dosages of ZOLGENSMA received by patients in this clinical

trial are unclear because of a change in the method for measuring the ZOLGENSMA concentration as well as decreases in the concentration of stored ZOLGENSMA over time.^{5,43}

At 24 months after infusion of ZOLGENSMA, 100% (12/12) of patients in the high-dose cohort were alive and free of permanent ventilation.⁵ The majority (92%; 11/12) of symptomatic patients in the high-dose cohort with SMA type 1 who were treated with ZOLGENSMA in START achieved or maintained Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores that exceeded 40 points.⁴⁵ CHOP INTEND was specifically developed to assess motor function in patients with SMA. The test consists of 16 measures of motor function, each scored on a scale of 0 to 4 points. The highest possible score is 64 points.⁵⁰ At the last assessment

(CONTINUED ON PAGE 10)

Table 4. (Continued) Clinical Studies of ZOLGENSMA® (onasemnogene abeparvovec-xioi)^{3-8,41-47,a}

| | STR1VE-US (NCT03306277) | SPR1NT (NCT03505099) | START (NCT02122952) |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary end point outcomes | <ul style="list-style-type: none"> 13 of 22 patients (59%) achieved sitting without support for ≥ 30 s at age 18 mo 20 of 22 patients (91%) were alive and free of permanent ventilation at age 14 mo | <ul style="list-style-type: none"> 14 of 14 patients (100%) with 2 <i>SMN2</i> copies sat independently by age 18 mo 15 of 15 patients (100%) with 3 <i>SMN2</i> copies could stand independently by age 24 mo | <ul style="list-style-type: none"> Of 275 AEs reported, 53 were serious, and 2 of these were treatment-related (asymptomatic serum aminotransferase elevations) |
| Secondary end point outcomes | <ul style="list-style-type: none"> 18 of 22 patients (82%) did not use ventilatory support at age 18 mo 9 of 22 patients (41%) met the composite end point of ability to thrive at age 18 mo » Ability to thrive is defined as achieving all of the following at 18 months of age⁶: <ul style="list-style-type: none"> > does not receive nutrition through mechanical support or other non-oral method > ability to tolerate thin liquids as demonstrated through a formal swallowing test > maintains weight | <ul style="list-style-type: none"> 14 of 14 patients (100%) with 2 <i>SMN2</i> copies were alive and free of permanent ventilation at age 14 mo 13 of 14 patients (93%) with 2 <i>SMN2</i> copies maintained weight at or above the third percentile without the need for non-oral/mechanical feeding support at all visits up to age 18 mo 14 of 15 patients (93%) with 3 <i>SMN2</i> copies walked independently for ≥ 5 steps at any visit up to age 24 mo | <ul style="list-style-type: none"> 12 of 12 patients (100%) in the high-dose cohort were alive and free of permanent ventilation at 24 mo post-treatment |

Continued

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Table 4. (Continued) Clinical Studies of ZOLGENSMA® (onasemnogene abeparvovec-xioi)^{3-8,41-47,a}

| | STRIVE-US (NCT03306277) | SPR1NT (NCT03505099) | START (NCT02122952) |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exploratory outcomes | <ul style="list-style-type: none"> • 19 of 22 patients (86%) achieved ≥ 1 motor milestone (BSID-III criteria) • Independent sitting (≥ 30 s) was achieved at a median age of 12.6 mo • Improvement of motor function by a mean of 14.6 points at 6 mo after treatment (CHOP INTEND criteria) | <ul style="list-style-type: none"> • 14 of 14 patients (100%) with 2 <i>SMN2</i> copies achieved a CHOP INTEND score > 40 • 14 of 14 patients (100%) with 2 <i>SMN2</i> copies demonstrated incremental gains on BSID gross and fine motor scales throughout the study duration, and all improved ≥15 points from baseline at any visit up to 18 mo of age • At 1 or more post-baseline visit(s), 14 of 14 patients with 2 <i>SMN2</i> copies had a scaled score ≥ 4.0 on both the gross motor and fine motor BSID assessments measured at the same visit • 9 patients (64%) with 2 <i>SMN2</i> copies achieved a scaled gross and fine motor score ≥ 4.0 at 18 mo • 15 of 15 patients (100%) with 3 <i>SMN2</i> copies were alive and free from permanent ventilation at 14 mo of age, and ventilator-free survival remained 100% at the end of the study • 10 of 15 patients (67%) with 3 <i>SMN2</i> copies were at or above the third reference percentile for weight at all study visits • 15 of 15 patients (100%) with 3 <i>SMN2</i> copies achieved a scaled score ≥ 4 on both the gross motor and fine motor subtests during at least 1 post-baseline visit • 10 of 10 patients (100%) with 3 <i>SMN2</i> copies who were assessed achieved a scaled score ≥ 4, with the median gross motor scaled score of 9 at the 24-mo visit | <ul style="list-style-type: none"> • 9 of 12 patients (75%) could sit without support for ≥ 30 s • 11 of 12 patients (92%) achieved or maintained a CHOP INTEND score > 40 • By 24 mo of age, the mean CHOP INTEND scores increased to 56.5 points from a baseline score of 37.0 |

AE, adverse event; BSID, Bayley Scale of Infant and Toddler Development; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; mo, month(s); mV, millivolt; s, second(s); SMA, spinal muscular atrophy; WHO, World Health Organization; wk, week(s); y, year(s).

^aGross motor function was measured by the BSID and compared to a standardized norm. The normal range for scores on the gross motor subtest is based on scaled score equivalents for unaffected patients: mean ±2 standard deviations (4-16 score [mean (SD), 10 (3); range, 1-19]).^{45,47}

^bOne patient was initially classified as presymptomatic and removed from the intent-to-treat (ITT) data set included in the Prescribing Information. The patient has been confirmed to be symptomatic at baseline and included in the final ITT analysis.⁵

^cSymptomatic patients showing clinical signs of SMA before 6 months of age were divided into 2 cohorts: a low-dose cohort (n = 3) and a high-dose cohort (n = 12).⁴³ The dosage received by patients in the low-dose cohort was approximately one-third of that received by patients in the high-dose cohort. However, the precise dosages of ZOLGENSMA received by patients in START are unclear because of a change in the method for measuring the ZOLGENSMA concentration as well as decreases in the concentration of stored ZOLGENSMA over time.^{5,43}

^dEvent-free survival was defined as absence of death or permanent ventilation (tracheostomy or ≥16 hours of daily non-invasive ventilation support for ≥14 days in the absence of acute reversible illness or perioperative ventilation).⁵

Important Safety Information for ZOLGENSMA® (onasemnogene abeparvovec-xioi)

BOXED WARNING: Serious Liver Injury and Acute Liver Failure

Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury, acute liver failure, and elevated aminotransferases can also occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing. Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated. If acute serious liver injury or acute liver failure is suspected, promptly consult a pediatric gastroenterologist or hepatologist.

Table 5. Long-Term Follow-Up Studies^{43,49}

| | START Long-Term Follow-Up (NCT03421977) | LT-002 Long-Term Follow-Up (NCT04042025) |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design | Ongoing, observational, long-term follow-up study of patients from START | Ongoing, observational, long-term follow-up study of patients who completed STR1VE-US, STR1VE-EU, STR1VE-AP, and SPR1NT |
| Patient population | <ul style="list-style-type: none"> • 3 patients from the START low-dose cohort • 10 patients from the START high-dose cohort | <ul style="list-style-type: none"> • 25 presymptomatic patients from SPR1NT • 24 symptomatic patients from STR1VE-EU • 12 symptomatic patients from STR1VE-US • 2 symptomatic patients from STR1VE-AP |
| Primary endpoints | <ul style="list-style-type: none"> • Safety/incidence of serious AEs and AEs of special interest • Motor milestone achievement • Ventilation support | <ul style="list-style-type: none"> • Safety/incidence of serious AEs and AEs of special interest • Ventilation support • In the initial 5-year follow-up phase, developmental milestones are assessed using a 10-item checklist (milestone achievement defined per WHO-MGRS or Bayley Scales of Infant and Toddler Development, 3rd ed), the achievement of new motor milestones, and maintenance of previously achieved motor milestones; change from baseline in HFMSE; requirement for nutrition support, physical examination, vital sign measurements, clinical laboratory assessments, cardiac assessments |
| Length of study | 15 y (ongoing; most recent data cutoff of May 23, 2022) | 15 years (ongoing; most recent data cutoff of May 23, 2022) |
| Primary endpoint outcomes | <ul style="list-style-type: none"> • No deaths or SAEs related to treatment were reported. The most frequently reported SAEs were acute respiratory failure, dehydration, and pneumonia (each in 5 patients, 38.5%) • As of May 2022, all 10 patients from the high-dose cohort who enrolled in the long-term follow-up were alive and free of permanent ventilation; the mean time since treatment was 6.9 (range, 6.4-7.5) years and the mean age at last follow-up was 7.1 (range, 6.6-7.9) years | <ul style="list-style-type: none"> • 61 patients had at least one milestone assessment in LT-002; all maintained previously achieved motor milestones • 22 patients achieved new motor milestones in LT-002 (presymptomatic, n = 6; symptomatic, n = 16) • All patients were alive with a mean (range) age at data cutoff of 3.7 (2.4-4.7) years. One (1.6%) patient required permanent ventilation via BiPAP ≥ 16 hours per day • 43 patients had both a baseline and at least one post-baseline HFMSE total score reported at LT-002 <ul style="list-style-type: none"> » In the presymptomatic cohort, 13 of 16 (81.3%) patients had improvements in HFMSE of ≥3 points from baseline, including 8 (50.0%) with > 10-point improvements » In the symptomatic cohort, 18 of 27 (66.7%) patients had improvements in HFMSE of ≥3 points from baseline, including 5 (18.5%) with > 10-point improvements • All patients in the presymptomatic cohort were free from any non-oral nutritional support (ie, G-tubes). 80% of the symptomatic cohort did not require feeding support at data cutoff • All patients in the presymptomatic cohort were independent of ventilatory support of any kind, including invasive support (ie, tracheostomy), BiPAP, or cough assist. 68.4% of the symptomatic cohort did not require ventilatory support (BiPAP and/or cough assist) • No deaths or TEAEs that resulted in study discontinuation were reported • No new safety signals were identified |

Continued

WARNINGS AND PRECAUTIONS

Systemic Immune Response

Patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response. Administer ZOLGENSMA to patients who are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

(CONTINUED FROM PAGE 7)

in START, patients in the high-dose cohort (the therapeutic dose) showed a mean CHOP INTEND score of 24.5 points higher than the baseline score.⁴⁶

The START LTFU is an ongoing study of patients treated with ZOLGENSMA from the phase 1 START trial (n = 13). The majority of these patients were included in the high-dose cohort in START (n = 10).⁴⁸ As of the May 2022 data analysis, the mean time since treatment was 6.9 years (range, 6.4-7.5 years), and the mean age at last follow-up was 7.1 years (range, 6.6-7.9) in the high-dose cohort (n = 10). All 10 patients from the high-dose cohort of START were alive and free from permanent ventilation. No treatment-related serious adverse events (AEs) were reported during the long-term follow-up.⁴³

Patients treated in phase 3 studies (STRIVE-US, STRIVE-EU [NCT03461289], STRIVE-AP [NCT03837184], SPRINT) are currently being evaluated in a 15-year, ongoing follow-up study of the safety and efficacy of ZOLGENSMA. Sixty-three patients who had been treated with ZOLGENSMA were enrolled (symptomatic SMA type 1, n = 38; presymptomatic, n = 25). All patients were alive and their mean age was 3.7 (2.4-4.7) years as of the May 2022 data cutoff; one patient required permanent ventilation. All patients maintained previously achieved motor milestones. A total of 48 patients achieved a new motor milestone or had already achieved all motor milestones assessed in

the parent study. Twenty patients had treatment-emergent adverse events (TEAEs); however, there were no deaths or TEAEs that resulted in study discontinuation.⁴³

The RESTORE registry is a prospective observational study designed to evaluate treatment patterns and long-term outcomes in patients with SMA. One analysis of the RESTORE data described clinical outcomes after monotherapy with ZOLGENSMA in patients with at least 4 copies of SMN2. Data from 12 children with 4 SMN2 copies and 7 with more than 4 SMN2 copies who had been treated with ZOLGENSMA were evaluated as of the data cutoff date of December 22, 2022. All were identified by newborn screening and all but 1 were asymptomatic at diagnosis; most were treated within 5 months of diagnosis. Of the 6 patients with at least 2 assessments of motor milestones, all 6 achieved a new motor milestone. Baseline assessments, duration of follow-up, and completion of data varied. Although 5 of the 19 children experienced at least 1 TEAE, no deaths or use of ventilatory or nutritional support were reported.⁴³

The biodistribution of ZOLGENSMA was assessed in postmortem samples obtained from 2 patients with SMA who were treated in the phase 3 STRIVE-US study and phase 3 STRIVE-EU study. The results revealed that SMN protein expression was present in the motor neurons. ZOLGENSMA crossed the blood-brain barrier and SMN protein was detected throughout the central nervous system and in the peripheral tissues.²⁹

Table 5. Long-Term Follow-Up Studies^{43,49}

| | START Long-Term Follow-Up (NCT03421977) | LT-002 Long-Term Follow-Up (NCT04042025) |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Secondary endpoint outcome | <ul style="list-style-type: none"> • 3 of 10 patients (30%) in the therapeutic-dose cohort achieved a new developmental milestone of standing with assistance » The remaining 7 patients maintained previously achieved milestones » 2 of the 3 new milestones were achieved without add-on therapy | Not applicable |

AE, adverse event; AESI adverse event of special interest; BiPAP, bilevel positive airway pressure; HFMSSE, Hammersmith Functional Motor Scale-Expanded; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

WARNINGS AND PRECAUTIONS (CONTINUED)

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

SAFETY CONSIDERATIONS AND MONITORING

Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur with ZOLGENSMA. Hepatotoxicity (which may be immune-mediated) is generally manifested as elevated alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] levels. Acute serious liver injury and acute liver failure, including fatal cases, have been reported with ZOLGENSMA use. To mitigate potential aminotransferase elevations, systemic corticosteroids need to be administered to all patients before and after ZOLGENSMA infusion as outlined in the Prescribing Information. Immune-mediated hepatotoxicity may require adjustment of the corticosteroid treatment regimen, including a longer duration, an increased dose, or a prolonged corticosteroid taper. Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, have been observed after ZOLGENSMA infusion, typically within the first 2 weeks after infusion. Cases of thrombotic microangiopathy (TMA) were reported to occur generally within the first 2 weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. The clinical importance of these findings is not known. Prior to and after infusion with ZOLGENSMA, laboratory testing is required. Baseline evaluations of liver function (clinical exam, AST, ALT, total bilirubin, albumin, prothrombin time, partial thromboplastin time [PTT], and international normalized ratio [INR]), creatinine, complete blood count (including hemoglobin and platelet count), and troponin-I are required. After infusion, liver function, platelet count, and troponin-I need to be monitored for at least 3 months as described in the Prescribing Information.⁵ Consultations and/or prompt referrals to specialists may be required based on signs, symptoms, and laboratory findings. Prescribers should refer to the Prescribing Information.⁵

To help mitigate the increased risk of a severe systemic immune response, ZOLGENSMA should only be administered to patients who are in a clinically stable overall baseline health state, considering factors such as hydration, nutritional status, and the absence of infection. Infusion of ZOLGENSMA should be postponed until the infection has resolved and the patient is deemed as clinically stable. No clinical signs or symptoms of infection should be present at the time of ZOLGENSMA infusion. There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. If a tumor develops in a patient receiving ZOLGENSMA, health care providers should contact and report the tumor to Novartis Gene Therapies, Inc.⁵

The most common AEs (incidence $\geq 5\%$) observed in clinical trials of ZOLGENSMA (N = 44) were elevated aminotransferases and vomiting, which occurred in 12 (27.3%) and 3 (6.8%) patients, respectively. Some patients with preexisting liver abnormalities reported acute serious liver injury and acute liver failure following ZOLGENSMA administration.⁵ Safety continues to be monitored.

ECONOMIC-RELATED VALUE OF EARLY TREATMENT WITH ZOLGENSMA

The Institute for Clinical and Economic Review (ICER) is a nonprofit organization that compiles and interprets data that can be used to guide health care and health-care-related industries in improving patient outcomes while managing costs.⁵¹ A long-term cost-effectiveness analysis was performed to compare the lifetime costs, life years gained, and quality-adjusted life years (QALYs) gained for best supportive care, treatment with ZOLGENSMA, and treatment with nusinersen. QALYs are calculated to assess the HRQOL of patients in terms of the quality and quantity of life.⁵¹ The use of QALY measurements in cost-effectiveness analysis aids in addressing clinical and public policy inquiries. Cost-effectiveness analysis is a method employed to assist decision-makers in comparing the costs and outcomes of various medical treatment options.⁵²

An analysis from a US health care sector perspective in the ICER review showed that in patients with SMA type 1, the cost per life year gained was around \$590,000 for nusinersen and \$182,000 for ZOLGENSMA; the cost of best supportive care was \$789,000.⁵¹ The ICER threshold prices shown in **Figure 1** are based on a one-time cost for ZOLGENSMA.^{51,53} Using the ultra-rare disease threshold of \$500,000 per QALY, ICER notes that ZOLGENSMA would be cost-effective at a price of up to \$5 million when using life-years gained vs best supportive care (**Table 6**).⁵¹

Data on the cost-effectiveness of treatment with ZOLGENSMA can be important. Families in which there are members with rare diseases retained commercial insurance for approximately 5 to 7 years, which is 1 year longer than families with members without rare diseases (**Figure 2**). These results were obtained from a retrospective study of insurance retention rates using data from 2007 to 2016 in the MarketScan database. The duration of subscriber retention can impact how payment arrangements are planned and structured for treatments that extend beyond the year of administration.⁵⁴

WARNINGS AND PRECAUTIONS (CONTINUED)

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported to occur generally within the first two weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor platelet counts closely as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

Figure 1. ZOLGENSMA® (onasemnogene abeparvovec-xioi) Threshold Prices for SMA Type 1⁵¹

| | Per QALY | Per LY gained |
|------------------------------|-------------|---------------|
| Threshold price at \$50,000 | — | — |
| Threshold price at \$100,000 | \$310,000 | \$710,000 |
| Threshold price at \$150,000 | \$899,000 | \$1,498,000 |
| Threshold price at \$200,000 | \$1,488,000 | \$2,287,000 |
| Threshold price at \$300,000 | \$2,666,000 | \$3,865,000 |
| Threshold price at \$500,000 | \$5,021,000 | \$7,020,000 |

- At \$2M, ZOLGENSMA would not be cost-effective at traditional US thresholds of \$100,000-\$150,000 per QALY.
 - » To be cost-effective at the \$150,000 threshold, the price must be < \$899,000.
- For rare diseases, ICER notes that payers may consider thresholds of up to \$500,000 per QALY.
 - » At a \$500,000 threshold, ZOLGENSMA would be cost-effective at a price of \$5M.

\$2M, 2 million dollars; \$5M, 5 million dollars; ICER, Institute for Clinical and Economic Review; LY, life year; QALY, quality-adjusted life year; SMA, spinal muscular atrophy.

Repurposed from Institute for Clinical and Economic Review. Spinraza and Zolgensma® for spinal muscular atrophy: effectiveness and value. Final evidence report. Published April 3, 2019. Updated May 24, 2019. Accessed October 5, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_052419.pdf

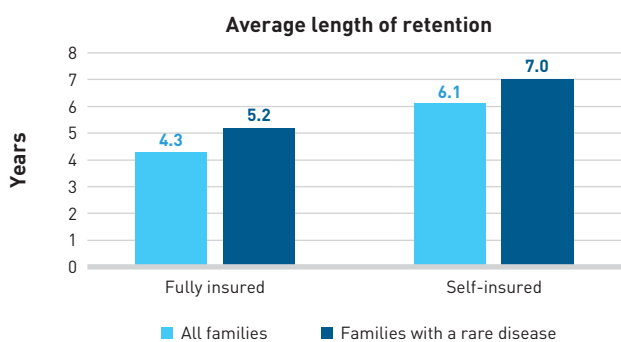
Table 6. ZOLGENSMA® (onasemnogene abeparvovec-xioi) vs Best Supportive Care for SMA Type 1⁵¹

| | BSC | Nusinersen | ZOLGENSMA |
|--------------------|-----------|-------------|-------------|
| Total costs | \$789,000 | \$3,884,000 | \$3,657,000 |
| Total LYs gained | 2.40 | 7.64 | 18.17 |
| Total QALYs gained | 0.46 | 3.24 | 12.23 |

BSC, best supportive care; LY, life year; SMA, spinal muscular atrophy; QALY, quality-adjusted life year.

Repurposed from Institute for Clinical and Economic Review. Spinraza and Zolgensma® for spinal muscular atrophy: effectiveness and value. Final evidence report. Published April 3, 2019. Updated May 24, 2019. Accessed October 5, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_052419.pdf

Figure 2. US Families With Rare Disease Retained Commercial Health Insurance for Approximately 5 to 7 Years, 1 Year Longer Than Those Without Rare Disease⁵⁴



WARNINGS AND PRECAUTIONS (CONTINUED)

Elevated Troponin-I

Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards. Consider consultation with a cardiologist if troponin elevations are accompanied by clinical signs or symptoms.

CONCLUSIONS

As of August 2023, more than 3500 patients globally have been treated with ZOLGENSMA including in clinical trials, managed access programs, and commercial use. Presymptomatic treatment of SMA improves patient outcomes supporting that treatment should not be delayed until symptoms appear. ZOLGENSMA targets the underlying root cause of SMA by enabling expression of functional SMN protein; this therapy can be administered pre- and post-symptomatically and exhibits durable effects. Treatment with ZOLGENSMA has been shown to be cost-effective. Furthermore, study results showed that early treatment of children with SMA using ZOLGENSMA improved survival, motor milestone achievements, and independence from nutritional and respiratory support when compared with the natural history of SMA. The safety profile of ZOLGENSMA has been evaluated in open-label clinical trials and observational long-term follow up. ZOLGENSMA has a boxed warning for serious liver injury and acute liver failure. The most common side effects reported in clinical studies were elevated aminotransferases and vomiting. Treatment with systemic corticosteroids, laboratory blood tests, and clinical examinations are required before infusion and for at least 3 months after treatment. Prescribers should refer to the Full Prescribing Information. •

REFERENCES

- Schorling DC, Pechmann A, Kirschner J. Advances in treatment of spinal muscular atrophy—new phenotypes, new challenges, new implications for care. *J Neuromuscul Dis.* 2020;7(1):1-13. doi:10.3233/JND-190424
- Salzman R, Cook F, Hunt T, et al. Addressing the value of gene therapy and enhancing patient access to transformative treatments. *Mol Ther.* 2018;26(12):2717-2726. doi:10.1016/j.yjthe.2018.10.017
- Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparovvec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the phase III SPRINT trial. *Nat Med.* 2022;28(7):1381-1389. doi:10.1038/s41591-022-01866-4
- Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparovvec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the phase III SPRINT trial. *Nat Med.* 2022;28(7):1390-1397. doi:10.1038/s41591-022-01867-3
- ZOLGENSMA. Prescribing information. Updated October 2023. Accessed November 29, 2023. https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf
- Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparovvec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STRIVE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol.* 2021;20(4):284-293. doi:10.1016/S1474-4422(21)00001-6
- Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med.* 2017;377(18):1713-1722. doi:10.1056/NEJMoa1706198
- Supplement to: Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparovvec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the phase III SPRINT trial. *Nat Med.* 2022;28(7):1390-1397. doi:10.1038/s41591-022-01867-3
- Lin C-W, Kalb SJ, Yeh W-S. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. *Pediatr Neurol.* 2015;53(4):293-300. doi:10.1016/j.pediatrneurol.2015.06.002
- Govoni A, Gagliardi D, Comi GP, Corti S. Time is motor neuron: therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. *Mol Neurobiol.* 2018;55(8):6307-6318. doi:10.1007/s12035-017-0831-9
- Tang R, Xu Z. Gene therapy: a double-edged sword with great powers. *Mol Cell Biochem.* 2020;474(1-2):73-81. doi:10.1007/s11010-020-03834-3
- Sugarmann EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* 2012;20(1):27-32. doi:10.1038/ejhg.2011.134
- If a genetic disorder runs in my family, what are the chances that my children will have the condition? MedlinePlus. Updated May 12, 2021. Accessed November 29, 2023. <https://medlineplus.gov/genetics/understanding/inheritance/riskassessment/>
- Mercuri E, Sumner CJ, Muntoni F, Darras BT, Finkel RS. Spinal muscular atrophy. *Nat Rev Dis Primers.* 2022;8(1):52. doi:10.1038/s41572-022-00380-8
- Cure SMA. Describing SMA. Accessed November 29, 2023. <https://www.curesma.org/describing-sma/>
- Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord.* 2018;28(3):208-215. doi:10.1016/j.nmd.2018.01.003
- Chan SHS, Wong CKH, Wu T, et al. Significant healthcare burden and life cost of spinal muscular atrophy: real-world data. *Eur J Health Econ.* 2023;24(8):1373-1382. doi:10.1007/s10198-022-01548-5
- Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neural Clin.* 2015;33(4):831-846. doi:10.1016/j.ncl.2015.07.004
- Newborn screening for spinal muscular atrophy. Cure SMA. Accessed November 29, 2023. <https://www.curesma.org/newborn-screening-for-sma/>
- Baby's First Test. Newborn screening 101. June 28, 2022. Accessed November 29, 2023. <https://www.babysfirsttest.org/newborn-screening/screening-101>
- Nicolau S, Waldrop MA, Connolly AM, Mendell JR. Spinal muscular atrophy. *Semin Pediatr Neurol.* 2021;37:100878. doi:10.1016/j.spen.2021.100878
- Jedrzejska M. Advances in newborn screening and presymptomatic diagnosis of spinal muscular atrophy. *Degener Neurol Neuromuscul Dis.* 2020;10:39-47. doi:10.2147/DNND.S246907
- Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have four copies of SMN2. *J Neuromuscul Dis.* 2020;7(2):97-100. doi:10.3233/JND-190468
- Soler-Botija C, Ferrer I, Gich I, Baiget M, Tizzano EF. Neuronal death is enhanced and begins during foetal development in type I spinal muscular atrophy spinal cord. *Brain.* 2002;125(pt 7):1624-1634. doi:10.1093/brain/awf155
- Stifani N. Motor neurons and the generation of spinal motor neuron diversity. *Front Cell Neurosci.* 2014;8:293. doi:10.3389/fncel.2014.00293
- Markowitz JA, Tinkle MB, Fischbeck KH. Spinal muscular atrophy in the neonate. *J Obstet Gynecol Neonatal Nurs.* 2004;33(1):12-20. doi:10.1177/0884217503261125
- Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. *Ther Clin Risk Manag.* 2019;15:1153-1161. doi:10.2147/TCRM.S172291
- Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis.* 2018;5(2):145-158. doi:10.3233/JND-180304
- Thomsen G, Burghes AHM, Hsieh C, et al. Biodistribution of onasemnogene abeparovvec DNA, mRNA and SMN protein in human tissue. *Nat Med.* 2021;27(10):1701-1711. doi:10.1038/s41591-021-01483-7
- Arnold WD, Burghes AHM. Spinal muscular atrophy: development and implementation of potential treatments. *Ann Neurol.* 2013;74(3):348-362. doi:10.1002/ana.23995
- Cardenas J, Menier M, Heitzer MD, Sproule DM. High healthcare resource use in hospitalized patients with a diagnosis of spinal muscular atrophy type 1 (SMA1): retrospective analysis of the Kids' Inpatient Database (KID). *Pharmacoecon Open.* 2019;3(2):205-213. doi:10.1007/s41669-018-0093-0
- Healthcare Cost and Utilization Project. Kids' Inpatient Database (KID) database documentation. February 18, 2022. Accessed November 29, 2023. <https://hcup-us.ahrq.gov/kidoverview.jsp>
- Belter L, Cruz R, Jarecki J. Quality of life data for individuals affected by spinal muscular atrophy: a baseline dataset from the Cure SMA Community Update Survey. *Orphanet J Rare Dis.* 2020;15(1):217. doi:10.1186/s13023-020-01498-2
- McMillan HJ, Gerber B, Cowling T, et al. Burden of spinal muscular atrophy (SMA) on patients and caregivers in Canada. *J Neuromuscul Dis.* 2021;8(4):553-568. doi:10.3233/JND-200610
- Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh W-S. Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. *BMC Neurol.* 2015;15:217. doi:10.1186/s12883-015-0473-3
- Spinraza. Prescribing information. Updated February 2023. Accessed November 29, 2023. https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf
- Evrysdi. Prescribing information. Updated October 2023. Accessed November 29, 2023. https://www.gene.com/download/pdf/evrysdi_prescribing.pdf

WARNINGS AND PRECAUTIONS (CONTINUED)

AAV Vector Integration and Risk of Tumorigenicity

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Cases of tumor have been reported in patients who received ZOLGENSMA post-approval; information on the cases is limited and causal relationship cannot be established. Report cases of tumor development in patients who received ZOLGENSMA to Novartis Gene Therapies, Inc. at 1-833-828-3947.

38. Baranello G, Darras BT, Day JW, et al.; FIREFISH Working Group. Risdiplam in type 1 spinal muscular atrophy. *N Engl J Med*. 2021;384(10):915-923. doi:10.1056/NEJMoa2009965
39. Zittersteijn HA, Gonçalves MAFV, Hoeben RC. A primer to gene therapy: progress, prospects, and problems. *J Inherit Metab Dis*. 2021;44(1):54-71. doi:10.1002/jimd.12270
40. Kichula EA, Proud CM, Farrar MA, et al. Expert recommendations and clinical considerations in the use of onasemnogene abeparovvec gene therapy for spinal muscular atrophy. *Muscle Nerve*. 2021;64(4):413-427. doi:10.1002/mus.27363
41. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparovvec in spinal muscular atrophy. *JAMA Neurol*. 2021;78(7):834-841. doi:10.1001/jamaneurol.2021.1272
42. Long-term follow-up study for patients from AVXS-101-CL-101 (START). ClinicalTrials.gov. Updated July 11, 2023. Accessed November 29, 2023. <https://classic.clinicaltrials.gov/ct2/show/NCT03421977>
43. Data on file. Novartis Gene Therapies, Inc. 2023.
44. Supplement to: Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparovvec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STRIVE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol*. 2021;20(4):284-293. doi:10.1016/S1474-4422(21)00001-6
45. Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (onasemnogene abeparovvec) for SMA1: comparative study with a prospective natural history cohort. *J Neuromuscul Dis*. 2019;6(3):307-317. doi:10.3233/JND-190403
46. Data on file. Novartis Gene Therapies, Inc. 2021.
47. Data on file. Novartis Gene Therapies, Inc. 2022.
48. Data on file. Novartis Gene Therapies, Inc. 2020.
49. Long-term follow-up study of patients receiving onasemnogene abeparovvec-xioi. ClinicalTrials.gov. Updated July 11, 2023. Accessed November 29, 2023. <https://clinicaltrials.gov/study/NCT04042025>
50. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010;20(3):155-161. doi:10.1016/j.nmd.2009.11.014
51. Institute for Clinical and Economic Review. Spinraza and Zolgensma® for spinal muscular atrophy: effectiveness and value. Final evidence report. Published April 3, 2019. Updated May 24, 2019. Accessed November 29, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_052419.pdf
52. Raisch DW. Understanding quality-adjusted life years and their application to pharmacoeconomic research. *Ann Pharmacother*. 2000;34(7-8):906-914. doi:10.1345/aph.19314
53. ICER comments on the FDA approval of Zolgensma for treatment of spinal muscular atrophy. Institute for Clinical and Economic Review. May 24, 2019. Accessed November 29, 2023. https://icer.org/news-insights/press-releases/icer_comment_on_zolgensma_approval/
54. Kuester MK, Jackson EA, Runyan BM, Pezalla EJ, Nussbaum SR. The effect of a pediatric rare disease on subscriber retention rates for commercial health insurers in the United States. *J Manag Care Spec Pharm*. 2019;25(2):186-195. doi:10.18553/jmcp.2018.18205

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence $\geq 5\%$) in clinical studies were elevated aminotransferases and vomiting.

© 2024 Novartis Gene Therapies, Inc.

Bannockburn, IL 60015
10/2023 US-ZOL-23-0039

