Clinical Reprints Available to Support the Use of ZOLGENSMA

zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion

Spinal muscular atrophy (SMA) is a progressive disease characterized by irreversible motor neuron loss. Early treatment can help maximize clinical benefit and improve patient outcomes.[1] Because there has been an ongoing release of data since the US Food and Drug Administration (FDA) approval of ZOLGENSMA® (onasemnogene abeparvovec-xioi), we've provided a source of clinical reprints to assist you in gaining a better understanding of the use and safety profile of ZOLGENSMA.

The following clinical reprints are grouped by topic and may help you support access for ZOLGENSMA.

The information contained in these publications should in no way be construed as a recommendation for the use of ZOLGENSMA in any manner other than as approved by the FDA and as described in the Prescribing Information for ZOLGENSMA. Please see Indication and Important Safety Information and click here for Full Prescribing Information, including Boxed WARNING for Serious Liver Injury and Acute Liver Failure.

SMA Studies

Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83(9):810-817.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC4155049/

Overview: This prospective cohort study describes the progression of SMA type 1 without treatment. Infants with SMA type 1 were followed for up to 36 months with serial clinical, motor function, laboratory, and electrophysiologic outcome assessments. The median age at reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support was 13.5 months (interquartile range 8.1-22.0 months).

Finkel RS, Mercuri E, Meyer OH, et al; for the SMA Care group. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*. 2018;28(3):197-207.

Link: https://www.nmd-journal.com/article/S0960-8966(17)31290-7/fulltext

Overview: This second part of a two-part series provides standard-of-care recommendations for SMA on pulmonary management and acute care issues. It also addresses other organ involvement in the severe forms of SMA, the role of medications, and ethical issues.

Kolb SJ, Coffey CS, Yankey JW, et al; for the NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. 2017;82(6):883-891.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC5776712/

Overview: The aim of this longitudinal, multicenter, prospective natural history was to understand disease progression in infantile-onset SMA as compared to age-matched control healthy infants and identify meaningful biomarkers. The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND) was used to measure motor functioning of natural history patients. The study developed definitive controlled data sets on the natural history of infantile-onset SMA.

Schroth M, Deans J, Arya K, et al. Spinal muscular atrophy update in best practices: recommendations for diagnosis considerations. *Neurol Clin Pract*. 2024;14(4):e200310. doi:10.1212/CPJ.0000000000200310

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC11195435/pdf/CPJ-2023-000383.pdf

Overview: This article reviews updated recommendations on SMA diagnosis and implementing newborn screening to facilitate early detection and access to treatment.

Clinical Reprints Available to Support the Use of ZOLGENSMA (cont)

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Patients With Four Copies of *SMN2*

Schorling DC, Becker J, Pechmann A, et al. Discrepancy in redetermination of *SMN2* copy numbers in children with SMA. *Neurology*. 2019;93(6):267-269.

Overview: To evaluate the accuracy of initial *survival motor neuron* 2 (*SMN2*) determinations in patients from Germany and Czech Republic, genetic testing was repeated with new samples from 20 patients with SMA using multiplex ligation-dependent probe amplification (MLPA).

Blaschek A, Kölbel H, Schwartz O, et al. Newborn screening for SMA – can a wait-and-see strategy be responsibly justified in patients with four *SMN2* copies? *J Neuromuscul Dis*. 2022;9(5):597-605.

Link: https://journals.sagepub.com/doi/10.3233/JND-221510

Overview: This prospective cohort study collected data on 21 patients with SMA and four copies of *SMN2* identified by newborn screening (NBS) between 2018 and 2021 in Germany. The study describes treatments and signs of SMA in patients up to four years of age.

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.

Overview: This determination of *SMN2* gene copy numbers was undertaken to establish genotype-phenotype correlations. An analysis of 625 unrelated Spanish patients' *SMN2* copy numbers was conducted to predict the course of their disease including motor function, life span, and SMA type.

Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of *SMN1* and *SMN2* based on real-time LightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genetics*. 2002;70(2):358-368.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC419987/

Overview: This publication explored a quantitative test for *survival motor neuron 1* (*SMN1*) and *SMN2*. A large number of patients with SMA were analyzed for *SMN2* copy numbers, and this was correlated with SMA type and duration of survival.

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.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC6004919/

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 4 copies of *SMN2*. *J Neuromuscul Dis*. 2020;7(2):97-100.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC7175931/

Overview: The 2018 publication details treatment recommendations for SMA outlined by the SMA Newborn Screening Multidisciplinary Working Group, convened by Cure SMA before the addition of SMA to the recommended uniform screening panel (RUSP).

The 2020 publication is a short communication that provides an update to the full recommendations published in 2018. Based on additional clinical data, real-world experience, and available therapeutic options, the Working Group updated their previous treatment recommendations to include "immediate treatment for infants diagnosed with SMA via NBS with 4 copies of *SMN2*."

Clinical Reprints Available to Support the Use of ZOLGENSMA (cont)

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Data on the Safety and Efficacy of ZOLGENSMA

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.*

Link: https://www.nejm.org/doi/10.1056/NEJMoa1706198

Overview: This study details the phase I clinical trial results of a single dose of ZOLGENSMA in 15 patients with SMA type 1. The primary outcome was safety and secondary outcomes included event-free survival. Motor function was measured using the CHOP INTEND and scores were compared with scores recorded in natural history studies.

Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparvovec in spinal muscular atrophy. *JAMA Neurol*. 2021;78(7):834-841.*

Link: https://jamanetwork.com/journals/jamaneurology/fullarticle/2780250

Overview: This ongoing study assesses the long-term safety of ZOLGENSMA and durability of response in infants with SMA type 1.

Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of *SMN2* (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol*. 2021;20(4):284-293.*

Overview: This was an open-label, single-arm, single-dose, phase III trial completed in 12 United States hospitals and universities in 22 patients younger than six months who were symptomatic with SMA type 1 and two copies of *SMN2*. The study group was compared with a historical cohort of 23 untreated infants. Patients were assessed until 18 months of age.

Day JW, Mendell JR, Mercuri E, et al. Clinical trial and postmarketing safety of onasemnogene abeparvovec therapy. *Drug Saf*. 2021;44(10):1109-1119. Erratum in: *Drug Saf*. 2022;45(2):191-192.*

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC8473343/

Overview: This is the first comprehensive assessment of overall safety data from seven clinical trials (n=102 patients) and postmarketing surveillance (n=665 reported adverse event cases) in patients treated with ZOLGENSMA. Analysis of adverse events of special interest included hepatotoxicity, thrombocytopenia, cardiac events, thrombotic microangiopathy (TMA), and ganglionopathy. Recommended mitigation strategies for each outlined ZOLGENSMA-related risk are included.

Chand DH, Zaidman C, Arya K, et al. Thrombotic microangiopathy following onasemnogene abeparvovec for spinal muscular atrophy: a case series. *J Pediatr*. 2021;231:265-268.*

Link: https://www.jpeds.com/article/S0022-3476(20)31466-9/fulltext

Overview: Three patients with SMA who developed TMA were reported in this publication.

Chand DH, Mitchell S, Sun R, et al. Safety of onasemnogene abeparvovec for patients with spinal muscular atrophy 8.5 kg or heavier in a global managed access program. *Pediatr Neurol*. 2022;132:27-32.*

Link: https://www.pedneur.com/article/S0887-8994(22)00082-0/fulltext

Overview: The Global Managed Access Program (GMAP) provided access to ZOLGENSMA for patients in countries where it was not approved. A total of 102 patients weighing ≥8.5 kg received ZOLGENSMA.

Clinical Reprints Available to Support the Use of ZOLGENSMA (cont)

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Data on the Safety and Efficacy of ZOLGENSMA (cont)

Chand D, Mohr F, McMillan H, et al. Hepatotoxicity following administration of onasemnogene abeparvovec (AVXS-101) for the treatment of spinal muscular atrophy. *J Hepatol*. 2021;74(3):560-566.*,†

Link: https://www.journal-of-hepatology.eu/article/S0168-8278(20)33748-X/fulltext

Overview: Liver-related adverse events and laboratory data from 325 patients with SMA who had received ZOLGENSMA through December 2019, in five clinical trials, a managed access program, a long-term registry (RESTORE), and through commercial use, were analyzed.

Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the phase III SPR1NT trial. *Nat Med*. 2022;28(7):1381-1389.*

Link: https://www.nature.com/articles/s41591-022-01866-4

Overview: This multicenter, single-arm study investigated the efficacy and safety of ZOLGENSMA for presymptomatic infants with bi-allelic *SMN1* gene mutations treated at ≤6 weeks of life.

Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of *SMN2* at risk for spinal muscular atrophy: the phase III SPR1NT trial. *Nat Med*. 2022;28(7):1390-1397.*

Link: https://www.nature.com/articles/s41591-022-01867-3

Overview: This multicenter, single-arm trial investigated the efficacy and safety of ZOLGENSMA for presymptomatic infants with bi-allelic *SMN1* mutations treated at ≤6 weeks of life.

Real-World Evidence

Finkel RS, Day JW, De Vivo DC, et al. RESTORE: a prospective multinational registry of patients with genetically confirmed spinal muscular atrophy – rationale and study design. *J Neuromuscul Dis*. 2020;7(2):145-152.†

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC7739962/pdf/jnd-7-jnd190451.pdf

Overview: This article introduces the RESTORE Registry, a prospective, multicenter, multinational observational registry of patients with SMA, and details the study design.

Tizzano EF, Quijano-Roy S, Servais L, et al. Outcomes for patients in the RESTORE Registry with spinal muscular atrophy and four or more *SMN2* gene copies treated with onasemnogene abeparvovec. *Eur J Pediatr Neurol*. 2024;53:18-24.†

Link: https://www.ejpn-journal.com/action/showPdf?pii=S1090-3798(24)00127-2

Overview: This analysis examined motor function, motor milestones achieved, adverse events, and the use of ventilatory or nutritional support among 19 patients who were treated with ZOLGENSMA monotherapy in the RESTORE Registry with four or more copies of *SMN2* as of the data cutoff of December 22, 2022.

Clinical Reprints Available to Support the Use of ZOLGENSMA (cont)

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Real-World Evidence (cont)

Servais L, Day JW, De Vivo DC, et al. Real-world outcomes in patients with spinal muscular atrophy treated with onasemnogene abeparvovec monotherapy: findings from the RESTORE Registry. *J Neuromuscul Dis*. 2024;11(2):425-442.†

Link: https://content.iospress.com/download/journal-of-neuromuscular-diseases/jnd230122?id=journal-of-neuromuscular-diseases%2Fjnd230122

Overview: An analysis of RESTORE Registry data as of May 23, 2022 describing outcomes among 168 patients treated with ZOLGENSMA monotherapy. The analysis included 98 patients identified by newborn screening and 70 through clinical diagnosis. The article describes outcomes including safety, event-free survival, motor milestones, and motor function measured by CHOP INTEND, Hammersmith Functional Motor Scale—Expanded (HFMSE), and Hammersmith Infant Neurological Examination Section 2 (HINE-2).

Waldrop MA, Karingada C, Storey MA, et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. *Pediatrics*. 2020;146(3):e2020079. doi:10.1542/peds.2020-0729

Link: https://publications.aap.org/pediatrics/article/146/3/e20200729/36757/

Overview: This is a retrospective review of the safety and early outcomes of ZOLGENSMA in 21 pediatric patients, aged one to 23 months, with SMA treated across four centers in Ohio. It included patients who had previously been treated with nusinersen and patients who were eight months of age or older at the time of treatment with ZOLGENSMA.

Waldrop MA, Chagat S, Storey M, et al. Continued safety and long-term effectiveness of onasemnogene abeparvovec in Ohio. *Neuromuscul Disord*. 2023;34:41-48.

Overview: This retrospective chart review reported three to five years of clinical follow-up of 19/21 of the initial Ohio cohort and safety and outcomes of an additional 27 children with SMA treated with ZOLGENSMA in one of five centers in Ohio between 2018 and 2023 with at least six months of follow-up data.

*This study and the associated clinical trials were sponsored by Novartis Pharmaceuticals Corporation (formerly AveXis, Inc.). Novartis was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

†The RESTORE Registry is sponsored by Novartis Pharmaceuticals Corporation.

Contact your Novartis Regional Account Associate Director (RAAD) with ZOLGENSMA-related questions

Name:

Title:

Email:

Phone:

Please see Indication and Important Safety Information on the next page and click here for Full Prescribing Information, including Boxed WARNING for Serious Liver Injury and Acute Liver Failure.

Indication and Important Safety Information

zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion

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 bi-allelic 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 (eg, 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.

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 (eg, hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first 2 weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Thrombotic Microangiopathy

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. 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.

Elevated Troponin I

Increases in cardiac troponin I levels have occurred following ZOLGENSMA infusion. Consider cardiac evaluation after ZOLGENSMA infusion and consult a cardiologist as needed.

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; a causal relationship has not been established based on tumor analysis. In some cases, limited information was available. Report cases of tumor development in patients who received ZOLGENSMA to Novartis Gene Therapies, Inc. at 1-833-828-3947.

Infusion-Related Reactions

Infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred with ZOLGENSMA infusion. Signs and symptoms may include rash, urticaria, vomiting, dyspnea, respiratory symptoms, and/or alterations in heart rate and blood pressure. Monitor patients during and after treatment with ZOLGENSMA. If an infusion-related reaction occurs, interrupt ZOLGENSMA infusion and administer supportive treatment to manage the infusion-related reaction as appropriate. Infusion of ZOLGENSMA may be resumed based on clinical assessment.

ADVERSE REACTIONS

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

Please click here for Full Prescribing Information.

Reference: 1. 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.

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