Clinical Reprints Available to Support the Use of ZOLGENSMA

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

The following clinical reprints can potentially help you support access for ZOLGENSMA® (onasemnogene abeparvovec-xioi).

- 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: The STR1VE study was an open-label, single-arm, single-dose, Phase 3 trial completed in 12 United States hospitals and universities in 22 eligible patients younger than 6 months who were symptomatic or presymptomatic for SMA Type 1 (a disabling mutation of *SMN1* [deletion or predicted protein null] and one or two copies of *SMN2*). The study group was compared with a historical cohort of 23 untreated infants with the same disease criteria from the Pediatric Neuromuscular Clinical Research (PNCR) data set. Patients received a single dose of onasemnogene abeparvovec over 30-60 minutes. During the outpatient follow-up, patients were assessed once per week, beginning at day 7 post-infusion for 4 weeks and then once per month until the end of the study (age 18 months or early termination). 13 (59%, 97.5% CI, 36-100) of 22 patients achieved functional independent sitting for 30 seconds or longer at the 18 months of age study visit (vs 0 of 23 patients in the untreated PNCR cohort; *P*<0.0001). 20 patients (91%, 95% CI, 79-100) survived free from permanent ventilation at age 14 months (vs 6 [26%, 8-44; *P*<0.0001] in the untreated PNCR cohort).

- 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.
  Overview: This study details the Phase I clinical trial result of a single dose of AVXS-101 in 15 patients with SMA Type 1.
  Patients were enrolled in 2 cohorts: Cohort 1 received a low dose and Cohort 2 received a high dose. The primary outcome was safety and the secondary outcome was the time until death or the need for permanent ventilatory assistance. Motor function of patients was measured using the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders), and scores were compared with scores recorded in natural-history 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.
  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. Of the 34 infants with SMA Type 1 who were enrolled in the study, 50% completed at least 12 months of follow-up. 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.
  Overview: This second part of a 2-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 spinal muscular atrophy, the role of medications, and ethical issues.

- 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.
  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.
  Overview: The 2018 publication details treatment recommendations for SMA outlined by the SMA NBS Multidisciplinary Working Group, convened by CureSMA 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*." The Working Group states that "the loss of even a small number of motor neurons is unacceptable when effective treatment is available, as this loss cannot be reversed after onset but can be prevented with earlier treatment."

- Kolb SJ, Coffey CS, Yankey JW, et al; for the NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. **Natural history of infantile-onset spinal muscular atrophy.** *Ann Neurol.* 2017;82(6):883-891.
  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. Twenty-six infants with SMA and 27 control infants aged <6 months were studied at 14 centers over 21 months within the NeuroNEXT (National Network for Excellence in Neuroscience Clinical Trials) Network. The 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.

Please see Indication and Important Safety Information, and accompanying Full Prescribing Information including Boxed Warning for Acute Serious Liver Injury and Acute Liver Failure.

Indication and Important Safety Information

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- Shababi M, Lorson CL, Rudnik-Schöneborn SS. **Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease?** *J Anat.* 2014;224(1):15-28.
  Overview: This article reviews clinical and experimental reports that link the loss of survival motor neuron (SMN) protein with peripheral organ deficiency and malfunction.

*Call your **Novartis Gene Therapies Regional Account Associate Director (RAAD)** for questions related to reimbursement.*

Indication

ZOLGENSMA is an adeno-associated virus 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 (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information

BOXED WARNING: Acute Serious Liver Injury and Acute Liver Failure

Acute serious liver injury, acute liver failure, and elevated aminotransferases can 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 (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion.

WARNINGS AND PRECAUTIONS

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.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported approximately 1 week after ZOLGENSMA infusion. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor for thrombocytopenia as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated.

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.

ADVERSE REACTIONS

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

Please see accompanying Full Prescribing Information.

NOVARTIS

Bannockburn, IL 60015

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