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

ZOLGENSMA® (onasemnogene abeparvovec-xioi)
Suspension for intravenous infusion
Initial U.S. Approval: 2019

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

- **Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. (5.1)**
- **Patients with pre-existing liver impairment may be at higher risk. (8.6)**
- **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 systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion (2.1) (2.3).**

INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) 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. (1)
Limitation of Use:

- The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated. (1, 6.2)
- The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated. (1, 14)

DOSAGE AND ADMINISTRATION

ZOLGENSMA is for single-dose intravenous infusion only (2).

- The recommended dosage of ZOLGENSMA is 1.1×10^{14} vector genomes (vg) per kg of body weight.
- Administer ZOLGENSMA as an intravenous infusion over 60 minutes. (2.1, 2.3)
- Starting one day prior to ZOLGENSMA infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30-day period of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose over the next 28 days. Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone. (2.1)

DOSAGE FORMS AND STRENGTHS

ZOLGENSMA is a suspension for intravenous infusion, supplied as single-use vials.
ZOLGENSMA is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. Each vial of ZOLGENSMA contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Thrombocytopenia: Monitor platelet counts before ZOLGENSMA infusion, and weekly for the first month and then every other week for the second and third month until platelet counts return to baseline. (2.3, 5.2)
- Elevated Troponin-I: Monitor troponin-I before ZOLGENSMA infusion, and weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline. (2.3, 5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting. (6)

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

USE IN SPECIFIC POPULATIONS

Pediatric use: Use of ZOLGENSMA in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until full-term gestational age is reached. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: ACUTE SERIOUS LIVER INJURY

- Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. (5.1)
- Patients with pre-existing liver impairment may be at higher risk. (8.6)
- 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 systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion (2.1) (2.3).

1 INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) 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.

Limitation of Use

- The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated [*see Adverse Reactions (6.2)*].
- The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence) has not been evaluated [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

For single-dose intravenous infusion only.

2.1 Dose and Administration

The recommended dose of ZOLGENSMA is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight.

Table 1: Dosing

Patient Weight Range (kg)	Dose Volume[a] (mL)
2.6 – 3.0	16.5
3.1 – 3.5	19.3
3.6 – 4.0	22.0
4.1 – 4.5	24.8
4.6 – 5.0	27.5
5.1 – 5.5	30.3
5.6 – 6.0	33.0
6.1 – 6.5	35.8
6.6 – 7.0	38.5
7.1 – 7.5	41.3
7.6 – 8.0	44.0
8.1 – 8.5	46.8
8.6 – 9.0	49.5
9.1 – 9.5	52.3
9.6 – 10.0	55.0
10.1 – 10.5	57.8
10.6 – 11.0	60.5
11.1 – 11.5	63.3
11.6 – 12.0	66.0
12.1 – 12.5	68.8
12.6 – 13.0	71.5
13.1 – 13.5[b]	74.3

[a] Dose volume is calculated using the upper limit of the patient weight range for pediatric patients less than 2 years of age between 2.6 kg and 13.5 kg

[b] Dose volume for pediatric patients less than 2 years of age weighing equal to or greater than 13.6 kg will require a combination of ZOLGENSMA kits.

- Prior to ZOLGENSMA infusion
  - Assess liver function [see Boxed Warning, Laboratory Testing and Monitoring to Assess Safety (2.3), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].
  - Measure platelet counts and troponin-I [see Laboratory Testing and Monitoring to Assess Safety (2.3), Warnings and Precautions (5.2)(5.3)]
  - Perform baseline testing for the presence of anti-AAV9 antibodies [see Laboratory Testing and Monitoring to Assess Safety (2.3), Adverse Reactions (6.2)].

- One day prior to ZOLGENSMA infusion, begin administration of systemic corticosteroids equivalent to oral prednisolone at 1 milligram per kilogram of body weight per day (mg/kg/day) for a total of 30 days.
- Administer ZOLGENSMA as a single-dose intravenous infusion through a venous catheter.

Follow the steps below for infusion:

1. Place a primary catheter into a vein (generally a peripheral vein in the arm or leg). Insertion of a back-up catheter is recommended.
2. Program syringe pump for saline priming, or prime tubing manually with saline.
3. Administer ZOLGENSMA as a slow infusion over 60 minutes. DO NOT INFUSE AS AN INTRAVENOUS PUSH OR BOLUS.
4. Flush line with saline following completion of infusion.
    - Monitor liver function by clinical examination and by laboratory testing on a regular basis [*see Laboratory Testing and Monitoring to Assess Safety (2.3)*].
        - At the end of the 30-day period of systemic corticosteroid treatment, check liver status clinically and by assessing ALT, AST, total bilirubin, and prothrombin time.
        - For patients with unremarkable findings (normal clinical exam, total bilirubin, and prothrombin time, and ALT and AST levels below 2 × upper limit of normal (ULN)), taper the corticosteroid dose over the next 28 days [*see Warnings and Precautions (5.1)*].
        - If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 × ULN and all other assessments return to normal range, and then taper the corticosteroid dose over the next 28 days.
        - Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.

2.2 Preparation

- Thaw ZOLGENSMA before use. The contents of the ZOLGENSMA kit will thaw in approximately 12 hours if placed in a refrigerator, or in approximately 4 hours if placed at room temperature. If thawed in a refrigerator, remove from refrigerator on day of dosing.
- When thawed, ZOLGENSMA is a clear to slightly opaque, colorless to faint white liquid, free of particles. Visually inspect vials for particulate matter and discoloration prior to infusion. Do not use vials if particulates or discoloration are present.
- DO NOT SHAKE.

- Draw the appropriate dose volume from all vials into a syringe, remove air from the syringe, cap the syringe, and deliver the syringe at room temperature to the patient infusion location.
- Use ZOLGENSMA within 8 hours of drawing into syringe. Discard the vector-containing syringe if the drug is not infused within the 8-hour timeframe.
- DO NOT REFREEZE.

2.3 Laboratory Testing and Monitoring to Assess Safety

Perform baseline anti-AAV9 antibody testing prior to ZOLGENSMA infusion. Retesting may be performed if anti-AAV9 antibody titers are reported as >1:50 [*see Dose and Administration (2.1)*].

Conduct the following tests at baseline and as directed below *[see Warnings and Precautions (5.1, 5.2, 5.3)]*:

- Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time) weekly for the first month; every other week for the second and third months, until results are unremarkable (normal clinical exam, total bilirubin, and prothrombin results, and ALT and AST levels below 2 × ULN).
- Platelet counts weekly for the first month, and then every other week for the second and third months, until platelet counts return to baseline.
- Troponin-I weekly for the first month, and then monthly for the second and third months, until troponin-I level returns to baseline.

3 DOSAGE FORMS AND STRENGTHS

ZOLGENSMA is a suspension for intravenous infusion.

ZOLGENSMA is provided in a kit containing 2 to 9 vials. Vials are provided in 2 fill volumes: 5.5 mL or 8.3 mL.

ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL, and each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

The intravenous dosage is determined by patient body weight, with a recommended dose of 1.1×10^{14} vg/kg for pediatric patients.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Serious Liver Injury and Elevated Aminotransferases

Acute serious liver injury can occur with ZOLGENSMA. Prior to ZOLGENSMA infusion, a patient with infantile-onset SMA had elevated AST and ALT of unknown etiology (gamma-glutamyl transferase (GGT), total bilirubin and prothrombin time were normal). The patient was treated under an expanded access program in the United States. The patient received corticosteroids equivalent to oral prednisolone at 1 mg/kg/day for approximately 30 days, followed by a 14-day taper. Approximately 7 weeks after receiving ZOLGENSMA, the patient became jaundiced. Laboratory testing was consistent with acute serious liver injury, with AST level approximately 80 × ULN and ALT level approximately 45 × ULN, total bilirubin approximately 4 × ULN, and plasma prothrombin time approximately 4 × ULN. Liver biopsy showed acute massive degeneration of hepatocytes, and massive mixed inflammatory infiltrate (primarily CD8-positive T lymphocytes). The patient recovered to baseline status after treatment with corticosteroids.

Administration of ZOLGENSMA may result in aminotransferase elevations. Two (2/44) patients in clinical trials had increased AST and ALT levels up to 48 × ULN after ZOLGENSMA infusion. These patients, who were otherwise asymptomatic with normal total bilirubin, were managed with systemic corticosteroids, and the abnormalities resolved without clinical sequelae.

Prior to ZOLGENSMA infusion, assess liver function by clinical examination and laboratory testing (hepatic aminotransferases [AST and ALT], total bilirubin level, and prothrombin time). Continue to monitor liver function for at least 3 months after ZOLGENSMA infusion (weekly for the first month, and then every other week for the second and third months, until results are unremarkable). [*see Laboratory Testing and Monitoring to Assess Safety (2.3)*] Administer systemic corticosteroid before and after ZOLGENSMA infusion [*see Dose and Administration (2.1)*].

5.2 Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed at different time points after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis afterwards (weekly for the first month; every other week for the second and third months until platelet counts return to baseline) [*see Laboratory Testing and Monitoring to Assess Safety (2.3)*].

5.3 Elevated Troponin-I

Transient increases in cardiac troponin-I levels (up to 0.176 µg/L) were observed following ZOLGENSMA infusion in clinical trials. The clinical importance of these findings is not known. However, cardiac toxicity was observed in animal studies *[see Animal Toxicology and/or Pharmacology (13.2)]*. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards (weekly for the first month, and then monthly for the second and third months until troponin-I level returns to baseline) [*see Laboratory Testing and Monitoring to Assess Safety (2.3)*].

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to ZOLGENSMA in four open-label studies conducted in the United States, including one completed clinical trial, two ongoing clinical trials, and one ongoing observational long-term follow-up study of the completed trial. A total of 44 patients with SMA received intravenous infusion of ZOLGENSMA, 41 patients at or above the recommended dose, and 3 patients at a lower dose. The patient population ranged in age from 0.3 months to 7.9 months at the time of infusion (weight range 3.0 kg to 8.4 kg).

The most frequent adverse reactions (incidence ≥ 5%) observed in the 4 studies are summarized in Table 2.

Table 2: Adverse Reactions Following Treatment with ZOLGENSMA (N = 44)

Adverse Reactions	**Patients n (%)**
Elevated aminotransferases[ab](> ULN)	12 (27.3%)
Vomiting	3 (6.8%)

ULN = upper limit of normal.

[a] Elevated aminotransferases include elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).

[b] In the completed clinical trial, one patient (the first patient infused in that study) was enrolled prior to the protocol amendment instituting administration of prednisolone before and after ZOLGENSMA infusion.

One patient in an ongoing non-United States clinical trial initially presented with respiratory insufficiency 12 days after ZOLGENSMA infusion and was found to have respiratory syncytial virus (RSV) and parainfluenza in respiratory secretions. The patient had episodes of serious hypotension, followed by seizures, and was found to have leukoencephalopathy (brain white matter defects) approximately 30 days after ZOLGENSMA infusion. The patient died after withdrawal of life support 52 days after ZOLGENSMA infusion.

6.2 Immunogenicity

In ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Perform baseline testing for the presence of anti-AAV9 antibodies prior to ZOLGENSMA infusion. Retesting may be performed if anti-AAV9 antibody titers are reported as > 1:50 [*see Dose and Administration (2.1), Laboratory Testing and Monitoring to Assess Safety (2.3)*].

Following ZOLGENSMA infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. In the completed clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients. Re-administration of ZOLGENSMA in the presence of high anti-AAV9 antibody titer has not been evaluated.

7 DRUG INTERACTIONS

Where feasible, adjust a patient's vaccination schedule to accommodate concomitant corticosteroid administration prior to and following ZOLGENSMA infusion [*see Dose and Administration (*2.1*)*]. Certain vaccines, such as MMR and varicella, are contraindicated for patients on a substantially immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent). Seasonal RSV prophylaxis is not precluded. (General Best Practice Guidelines for Immunization [www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf], eds2017)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data regarding ZOLGENSMA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with ZOLGENSMA.

In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There is no information available on the presence of ZOLGENSMA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOLGENSMA and any potential adverse effects on the breastfed child from ZOLGENSMA or from the underlying maternal condition.

8.4 Pediatric Use

Administration of ZOLGENSMA to premature neonates before reaching full-term gestational age is not recommended, because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until the corresponding full-term gestational age is reached.

There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for anti-AAV9 antibodies.

The safety of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg) [*see Adverse Reactions (6)*].

The efficacy of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg) [*see Clinical Studies (14)*].

8.6 Hepatic Impairment

One patient who received ZOLGENSMA developed acute serious liver injury; that patient had elevated aminotransferase levels prior to ZOLGENSMA infusion. In clinical trials, elevation of aminotransferases was observed in patients following ZOLGENSMA infusion [*see Warnings and Precautions (5.1)*].

11 DESCRIPTION

ZOLGENSMA is a suspension of an adeno-associated viral vector-based gene therapy for intravenous infusion. It is a recombinant self-complementary AAV9 containing a transgene encoding the human survival motor neuron (SMN) protein, under the control of a cytomegalovirus enhancer/chicken-β-actin hybrid promoter.

ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL. Each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL and the excipients 20 mM Tris (pH 8.0), 1 mM magnesium chloride ($MgCl_2$), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188. ZOLGENSMA is packaged as a sterile suspension and contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZOLGENSMA is a recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein. SMA is caused by a bi-allelic mutation in the *SMN1* gene, which results in insufficient SMN protein expression. Intravenous administration of ZOLGENSMA that results in cell transduction and expression of the SMN protein has been observed in two human case studies *[see Pharmacokinetics (12.3)*].

12.2 Pharmacodynamics

There are no clinically relevant pharmacodynamics data for ZOLGENSMA.

12.3 Pharmacokinetics

Vector shedding after infusion with ZOLGENSMA was investigated at multiple time points during the completed clinical trial. Samples of saliva, urine and stool were collected the day after infusion, weekly through Day 30, and then monthly through Month 12 and every 3 months thereafter. Samples from 5 patients were used for ZOLGENSMA vector DNA shedding analysis through the Month 18 visit.

Vector DNA was shed in saliva, urine and stool after infusion of ZOLGENSMA, with much higher concentrations of vector DNA found in stool than in saliva or urine. The vector DNA concentration in saliva was low on Day 1 after infusion and declined to undetectable levels within 3 weeks. In urine, the vector DNA concentration was very low on Day 1 after infusion and declined to undetectable levels within 1 to 2 weeks. In stool, the vector DNA concentration was much higher than in saliva or urine for 1 to 2 weeks after infusion and declined to undetectable levels by 1 to 2 months after infusion.

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of ZOLGENSMA at the dose of 1.1×10^{14} vg/kg. Both cases showed that the highest levels of vector DNA were found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph node, skeletal muscles, peripheral nerves, kidney, lung, intestines, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalized SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the effects of ZOLGENSMA on carcinogenesis, mutagenesis or impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies conducted in neonatal mice, dose-dependent cardiac and hepatic toxicities were observed following intravenous administration of ZOLGENSMA. ZOLGENSMA-related findings in the myocardium, at doses of 7.9×10^{13} vg/kg and higher, included slight to mild mononuclear cell inflammation accompanied by edema, slight to mild fibrosis, and scattered myocardial cell degeneration/regeneration. Additional cardiac findings at dose levels of 1.5×10^{14} vg/kg and higher included minimal to moderate atrial thrombosis and slight to marked atrial dilation. Liver findings included hepatocellular hypertrophy, Kupffer cell activation, perinuclear vacuolation, and scattered hepatocellular necrosis. Target organ toxicity in the heart and liver was associated with mortality at dose levels of 2.4×10^{14} vg/kg and above, approximately 2.2-fold higher than the recommended clinical dose level.

14 CLINICAL STUDIES

The efficacy of ZOLGENSMA in pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene was evaluated in an open-label, single-arm clinical trial (ongoing) and an open-label, single-arm, ascending-dose clinical trial (completed). Patients experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic *SMN1* gene deletions, 2 copies of the *SMN2* gene, and absence of the c.859G>C modification in exon 7 of *SMN2* gene (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of ≤ 1:50, measured by ELISA. In both trials, ZOLGENSMA was delivered as a single-dose intravenous infusion.

Efficacy was established on the basis of survival, and achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). CHOP-INTEND is an assessment of motor skills in patients with infantile-onset SMA.

The ongoing clinical trial enrolled 21 patients (10 male and 11 female) with infantile-onset SMA. Before treatment with ZOLGENSMA, none of the 21 patients required non-invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., no need for non-oral nutrition). The mean CHOP-INTEND score at baseline was 31.0 (range 18 to 47). All the patients received 1.1×10^{14} vg/kg of ZOLGENSMA. The mean age of the 21 patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months).

As of the March 2019 data cutoff, 19 patients were alive without permanent ventilation (i.e., event-free survival) and were continuing in the trial, while one patient died at age 7.8 months due to disease progression, and one patient withdrew from the study at age 11.9 months. The 19 surviving patients who were continuing in the trial ranged in age from 9.4 to 18.5 months. By the data cutoff, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation, one of the study's co-primary efficacy endpoints. In addition to survival, assessment of the other co-primary efficacy endpoint found that 10 of the 21 patients (47.6%) achieved the ability to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 months). Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive (i.e., being alive without permanent ventilation) beyond 14 months of age. In addition, 16 of the 19 patients had not required daily NIV use.

Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of ZOLGENSMA.

The completed clinical trial enrolled 15 patients (6 male and 9 female) with infantile-onset SMA, 3 in a low-dose cohort and 12 in a high-dose cohort. At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months), and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. The dosage received by patients in the

low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of ZOLGENSMA received by patients in this completed clinical trial are unclear due to a change in the method of measuring ZOLGENSMA concentration, and to decreases in the concentration of stored ZOLGENSMA over time. The retrospectively-estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg.

By 24 months following ZOLGENSMA infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. None of the patients in the low-dose cohort were able to sit without support, or to stand or walk; in the high-dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for ≥ 30 seconds, and 2 patients (16.7%) were able to stand and walk without assistance. Comparison of the results of the low-dose cohort to the results of the high-dose cohort shows a dose-response relationship that supports the effectiveness of ZOLGENSMA.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZOLGENSMA is shipped frozen (≤ -60°C [-76°F]) in 10 mL vials with 2 fill volumes (either 5.5 mL or 8.3 mL).

ZOLGENSMA is provided as a customized kit to meet dosing requirements for each patient [*see Dose and Administration (2.1)*], with each kit containing:

- Two (2) to nine (9) vials of ZOLGENSMA (see below)
- One alcohol wipe per vial

Kit sizes and National Drug Codes (NDC) are provided in Table 3.

Table 3: ZOLGENSMA Kit Sizes

Patient Weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total Vials per Kit	NDC Number
2.6 – 3.0	0	2	2	71894-120-02
3.1 – 3.5	2	1	3	71894-121-03
3.6 – 4.0	1	2	3	71894-122-03
4.1 – 4.5	0	3	3	71894-123-03
4.6 – 5.0	2	2	4	71894-124-04
5.1 – 5.5	1	3	4	71894-125-04
5.6 – 6.0	0	4	4	71894-126-04
6.1 – 6.5	2	3	5	71894-127-05
6.6 – 7.0	1	4	5	71894-128-05
7.1 – 7.5	0	5	5	71894-129-05
7.6 – 8.0	2	4	6	71894-130-06
8.1 – 8.5	1	5	6	71894-131-06
8.6 – 9.0	0	6	6	71894-132-06
9.1 – 9.5	2	5	7	71894-133-07
9.6 – 10.0	1	6	7	71894-134-07
10.1 – 10.5	0	7	7	71894-135-07
10.6 – 11.0	2	6	8	71894-136-08
11.1 – 11.5	1	7	8	71894-137-08
11.6 – 12.0	0	8	8	71894-138-08
12.1 – 12.5	2	7	9	71894-139-09
12.6 – 13.0	1	8	9	71894-140-09
13.1 – 13.5	0	9	9	71894-141-09

[a] Vial nominal concentration is 2.0×10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL.
[b] Vial nominal concentration is 2.0×10^{13} vg/mL and contains an extractable volume of not less than 8.3 mL.

16.2 Storage and Handling

- Product is shipped and delivered frozen (≤ -60 °C [-76 °F]) in clear vials.
- Upon receipt, immediately place the kit in a refrigerator at 2°C to 8°C (36°F to 46°F).
- ZOLGENSMA is stable for 14 days from receipt when stored at 2°C to 8°C (36°F to 46°F).
- **DO NOT REFREEZE**.
- Must use within 14 days of receipt.

17 PATIENT COUNSELING INFORMATION

Acute Serious Liver Injury and Elevated Aminotransferases

Inform caregivers that ZOLGENSMA could increase liver enzyme levels and cause acute serious liver injury. Inform caregivers that patients will receive an oral corticosteroid medication before and after infusion with ZOLGENSMA, and will undergo regular blood tests to monitor liver

function. Advise caregivers to contact their healthcare provider immediately if the patient's skin and/or whites of the eyes appear yellowish, or if the patient misses a dose of corticosteroid or vomits it up.

Vaccination Before and After Infusion with ZOLGENSMA

Advise caregivers to consult with their healthcare provider to determine if adjustments to the patient's vaccination schedule are necessary during corticosteroid use. Inform caregivers that where feasible, the vaccination schedule should be adjusted appropriately to accommodate treatment with corticosteroid. Prophylaxis against respiratory syncytial virus is recommended. Please consult your health care provider.

Caregivers should be aware that a viral respiratory infection (e.g., cold, flu, or bronchiolitis) before or after ZOLGENSMA infusion could lead to more serious complications. Advise caregivers of the signs of a possible viral respiratory infection, such as coughing, wheezing, sneezing, runny nose, sore throat or fever. Caregivers should contact their healthcare provider immediately if they see any of these symptoms.

Thrombocytopenia

Inform caregivers that ZOLGENSMA could decrease blood platelet count and increase the risk of bruising or bleeding. Advise caregivers to seek medical attention if the patient experiences unexpected bruising or bleeding.

Vector Shedding

Temporary vector shedding of ZOLGENSMA occurs primarily through body waste. Advise caregivers on the proper handling of patient feces; recommended procedures include sealing disposable diapers in disposable trash bags and then discarding into regular trash. Provide instructions to caregivers and family members regarding proper hand hygiene when coming into direct contact with patient body waste. These precautions should be followed for one month after ZOLGENSMA infusion.

Manufactured by, Packed by, Distributed by:

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SMA003-F19-ZOL-CPI-US