NOVARTIS

1 Tradename

ZOLGENSMA® Suspension for intravenous infusion

2 Description and composition

Pharmaceutical form

Zolgensma is a suspension for intravenous infusion supplied as single-use vials. When thawed, Zolgensma is a clear to slightly opaque, colorless to faint white solution.

Active substance

Each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg). Vials will contain an extractable volume of not less than either 5.5 mL or 8.3 mL. The total number of vials and combination of fill volumes in each finished pack will be customized to meet dosing requirements for individual patients depending on their weight.

Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human survival motor neuron (SMN) gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter. Onasemnogene abeparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

Excipients

Tromethamine

Magnesium chloride

Sodium chloride

Poloxamer 188

Hydrochloric Acid (for pH adjustment)

Water for Injection

3 Indications

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 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or
- with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.

4 Dosage regimen and administration

Zolgensma should only be infused by a healthcare professional. Zolgensma should be initiated and administered in a hospital setting and supervised by a physician experienced in the management of patients with SMA.

In order to improve the traceability of Cell, Tissue and Gene Therapy Product (CTGTP), the name and the batch number of the administered product should be clearly recorded.

An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after infusion of Zolgensma, thus patients should not be re-dosed with Zolgensma.

Zolgensma is for a single treatment only.

Dosage regimen

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg)/kg.

The Zolgensma kit consists of 2 vial sizes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vg/mL. The appropriate Zolgensma dose and kit is determined by patient body weight (Table 4-1).

Table 4-1 Recommended dosing based on patient body weight

Patient weight range (kg)	Dose (vg)	Total volume of dose[a] (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9.9×10^{14}	49.5
9.1 – 9.5	1.05×10^{15}	52.3
9.6 – 10.0	1.10×10^{15}	55.0
10.1 – 10.5	1.16×10^{15}	57.8
10.6 – 11.0	1.21×10^{15}	60.5
11.1 – 11.5	1.27×10^{15}	63.3
11.6 – 12.0	1.32×10^{15}	66.0
12.1 – 12.5	1.38×10^{15}	68.8
12.6 – 13.0	1.43×10^{15}	71.5
13.1 – 13.5	1.49×10^{15}	74.3
13.6 – 14.0	1.54×10^{15}	77.0
14.1 – 14.5	1.60×10^{15}	79.8
14.6 – 15.0	1.65×10^{15}	82.5
15.1 – 15.5	1.71×10^{15}	85.3
15.6 – 16.0	1.76×10^{15}	88.0
16.1 – 16.5	1.82×10^{15}	90.8
16.6 – 17.0	1.87×10^{15}	93.5
17.1 – 17.5	1.93×10^{15}	96.3
17.6 – 18.0	1.98×10^{15}	99.0
18.1 – 18.5	2.04×10^{15}	101.8
18.6 – 19.0	2.09×10^{15}	104.5
19.1 – 19.5	2.15×10^{15}	107.3
19.6 – 20.0	2.20×10^{15}	110.0
20.1 – 20.5	2.26×10^{15}	112.8

Patient weight range (kg)	Dose (vg)	Total volume of dose[a] (mL)
20.6 – 21.0	2.31×10^{15}	115.5

[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 21.0 kg.

Due to the increased risk of serious systemic immune response, it is recommended that patients are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection) prior to Zolgensma infusion. Zolgensma should be postponed in patients with infections until the infection has resolved and the patient is clinically stable. Clinical signs or symptoms of infection should not be evident at the time of Zolgensma infusion (see section 6 Warnings and precautions).

Laboratory Testing and Monitoring to Assess Safety

Prior to Zolgensma infusion, the following laboratory tests should be conducted at baseline (see section 6 Warnings and precautions):

- AAV9 antibody testing (retesting may be performed if AAV9 antibody titers are reported as above 1:50)
- Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, partial thromboplastin time (PTT), and international normalized ratio (INR)
- Creatinine
- Complete blood count (including hemoglobin and platelet count)
- Troponin-I

After Zolgensma infusion, the following laboratory tests should be conducted on a regular basis (see section 6 Warnings and precautions):

- Liver function: ALT, AST, and total bilirubin
- Platelet counts

Systemic Corticosteroid Treatment Pre- and Post-Zolgensma Infusion

An immune response to the AAV9 capsid will occur after administration of Zolgensma. This can lead to elevations in liver aminotransferases, elevations of troponin I, or decreased platelet counts (see section 6 Warnings and precautions and section 7 Adverse drug reactions). To dampen the immune response, immunomodulation with corticosteroids is recommended. All patients should receive systemic corticosteroids given orally before and after dosing Zolgensma (see section 6 Warnings and precautions). Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Zolgensma infusion (see sections 6 Warnings and precautions and 8 Interactions).

Treatment with Systemic Corticosteroid Prior to Zolgensma Infusion

Starting 24 hours prior to Zolgensma infusion, pre-treat with oral prednisolone at a dose of 1 mg/kg/day (or equivalent if another corticosteroid is used).

Continued Treatment with Systemic Corticosteroid/Liver Function Monitoring Following Zolgensma Infusion

- Prednisolone should be administered daily at 1 mg/kg/day (or equivalent if another corticosteroid is used) for 30 days (including the day of administration of Zolgensma) following infusion with Zolgensma.

- At the end of the 30-day period of systemic corticosteroid treatment, check liver status clinically and by assessing ALT, AST, and total bilirubin Liver function should be monitored for at least 3 months following Zolgensma infusion, and at other times as clinically indicated (see section 6 Warnings and precautions).
- Promptly clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness.
- For patients with unremarkable findings (normal clinical exam, total bilirubin, and ALT and AST levels below 2 × ULN) at the end of the 30-day period: Taper the corticosteroid dose over the next 28 days. Systemic corticosteroids should not be stopped abruptly, rather tapered gradually (see section 6 Warnings and precautions).
- 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 or longer if needed. Systemic corticosteroids should not be stopped abruptly, rather tapered gradually (see section 6 Warnings and precautions).
- Promptly consult a pediatric gastroenterologist or hepatologist if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone. If oral corticosteroid therapy is not tolerated or not effective, intravenous corticosteroids may be considered as clinically indicated (see section 6 Warnings and precautions).

Variance from these recommendations is at the discretion of the treating physician. If another corticosteroid is used by the physician in place of prednisolone, similar considerations and approach to taper the corticosteroid dose after 30 days following infusion with Zolgensma should be taken as appropriate.

Special populations

Renal impairment

The safety and efficacy of Zolgensma have not been established in patients with renal impairment and Zolgensma therapy should be carefully considered. A dose adjustment should not be considered.

Hepatic impairment

Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) >2 × ULN have not been studied in clinical studies with Zolgensma. Zolgensma therapy should be carefully considered in patients with hepatic impairment (see section 6 Warnings and precautions). A dose adjustment should not be considered.

Pediatric patients

The safety and efficacy of Zolgensma in premature neonates before reaching full-term gestational age have not been established. Administration of Zolgensma should be carefully considered because concomitant treatment with corticosteroids may adversely affect neurological development.

There is limited experience in patients 2 years of age and older or with body weight above 13.5kg. The safety and efficacy of Zolgensma in these patients have not been established.

Method of administration

Zolgensma is for single-dose intravenous infusion only.

Preparation of Zolgensma

- Zolgensma should be prepared aseptically.
- Thaw Zolgensma:
  - 9-vial kit: in the refrigerator (2°C to 8°C) for approximately 12 hours, or at room temperature (20°C to 25°C) for approximately 4 hours
  - 14-vial kit: in the refrigerator (2°C to 8°C) for approximately 16 hours, or at room temperature (20°C to 25°C) for approximately 6 hours
  - Do not use Zolgensma unless thawed.
  - If thawed in the refrigerator, remove Zolgensma 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.
  - Immediately prior to dosing, draw the appropriate dose volume from all vials into the syringe, remove air from syringe, cap syringe and deliver to patient infusion location.
  - Once dose is drawn into the syringe, it must be used within 8 hours. Discard the vector-containing syringe if not infused within the 8-hour timeframe.
  - DO NOT REFREEZE.

Intravenous Infusion Instructions

- Place a primary catheter in a peripheral vein (arm or leg).
- Insertion of a back-up catheter is recommended.
- Program syringe pump for saline priming, or prime tubing manually with saline.
- Administer Zolgensma as a slow infusion over 60 minutes. Do not infuse as a rapid intravenous injection or bolus.
- Following completion of infusion, flush line with saline.
- Seal used Zolgensma vials in a biohazard bag and discard in biohazard waste containers for disposal.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 2 Description and composition).

6 Warnings and precautions

Advanced SMA

Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of Zolgensma in symptomatic patients depends on the degree of disease burden at the time of treatment, with earlier treatment resulting in potential higher benefit.

Progressive motor neuron loss is irreversible. The treating physician should consider that the benefit is seriously reduced in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients not able to swallow.

The benefit/risk profile of Zolgensma in patients with advanced SMA kept alive through permanent ventilation and without the ability to thrive is not established.

Hepatotoxicity

- Administration of AAV vector may result in aminotransferase elevations, which may be serious.
- Acute serious liver injury and acute liver failure have occurred with Zolgensma. Cases of acute liver failure with fatal outcomes have been reported.
- Patients with pre-existing hepatic impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury/acute liver failure.
- Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been studied in clinical trials with Zolgensma.
- Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., AST, ALT, total bilirubin, albumin, prothrombin time, PTT and INR).
- In order to mitigate potential aminotransferase elevations, a systemic corticosteroid should be administered to all patients before and after Zolgensma infusion (see section 4 Dosage regimen and administration).
- Liver function (ALT, AST, total bilirubin) should be monitored for at least 3 months after infusion, and at other times as clinically indicated (see section 4 Dosage regimen and administration).
- Promptly clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness.
- In case hepatic injury is suspected, further testing is recommended (e.g., albumin, prothrombin time, PTT and INR).
- The risks and benefits of Zolgensma therapy should be carefully considered in patients with pre-existing hepatic impairment.

Immune-mediated hepatotoxicity generally manifested as elevated ALT and/or AST levels. Acute serious liver injury and acute liver failure, including fatal cases, have been reported with Zolgensma use. Immune-mediated hepatotoxicity may require adjustment of the corticosteroid treatment regimen including longer duration, increased dose, or prolongation of the corticosteroid taper (see sections 4 Dosage regimen and administration and 7 Adverse drug reactions).

AST, ALT, total bilirubin, albumin, prothrombin time, PTT and INR should be assessed before Zolgensma infusion. AST, ALT and total bilirubin should be monitored weekly for the month after Zolgensma infusion and during the corticosteroid taper period. If the patient is clinically stable with unremarkable findings at the end of the corticosteroid taper period, liver function should continue to be monitored every two weeks for another month. Tapering of systemic corticosteroids should not be considered until AST/ALT levels are less than 2 × ULN (see section 4 Dosage regimen and administration).

Systemic immune response

Due to the increased risk of serious systemic immune response, it is recommended that patients are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection) prior to Zolgensma infusion. Zolgensma should be postponed in patients with infections until the infection has resolved and the patient is clinically stable. Clinical signs or symptoms of infection should not be evident at the time of Zolgensma infusion (see section 4 Dosage regimen and administration),

Infection, either acute (e.g. respiratory) or chronic uncontrolled, could increase the risk of serious systemic immune response, potentially resulting in more severe clinical courses of the infection. Patients with infection were excluded from participation in Zolgensma clinical trials. Increased vigilance in the prevention, monitoring, and management of infection is recommended before and after Zolgensma infusion. Seasonal prophylaxis against respiratory syncytial virus (RSV) is recommended and should be up-to-date.

The treating physician should be aware of the possibility of adrenal insufficiency related to longer duration of treatment with corticosteroids or increased dose.

Immunogenicity

In Zolgensma clinical trials, confirmation of AAV9 antibody titers at or below 1:50 was required prior to infusion. It has not been established whether infusion of Zolgensma may represent a risk for an immune response for patients with pre-existing AAV9 antibodies at higher titers. The safety and efficacy of Zolgensma has not been established in patients with baseline AAV9-antibody titers above 1:50. Patients should be tested for the presence of AAV9 antibodies prior to infusion with Zolgensma. Retesting may be performed if AAV9 antibody titers are reported as above 1:50. An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after infusion of Zolgensma.

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 (see section 7 Adverse drug reactions).

Platelet counts should be obtained before Zolgensma infusion and should be closely monitored for significant decreases within the first two weeks following infusion and on a regular basis afterwards; at least weekly for the first month and every other week for the second and third months until platelet counts return to baseline.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy (TMA) have been reported to occur generally within the first two weeks after Zolgensma infusion in the post-marketing setting (see section 7 Adverse drug reactions). Thrombotic microangiopathy is characterized by thrombocytopenia,

microangiopathic hemolytic anemia, and acute kidney injury. Concurrent immune system activation (e.g., infections, vaccinations) was identified as a contributing factor in some cases.

Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes.

Thrombocytopenia is a key feature of TMA, therefore platelet counts should be closely monitored for significant decreases within the first two weeks following infusion and on a regular basis afterwards (see sub-section Thrombocytopenia), as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, or decreased urine output. In case these signs and symptoms occur in the presence of thrombocytopenia, further diagnostic evaluation for hemolytic anemia and renal dysfunction should be promptly undertaken. If clinical signs, symptoms and/or laboratory findings consistent with TMA occur, a pediatric hematologist and/or pediatric nephrologist should be consulted immediately to manage TMA as clinically indicated.

Elevated troponin-I

Increases in cardiac troponin-I levels following infusion with Zolgensma were observed (see section 7 Adverse drug reactions). Elevated troponin-I levels found in some patients may indicate potential myocardial tissue injury. Based on these findings and the observed cardiac toxicity in mice, troponin-I levels should be obtained before Zolgensma infusion and monitored as clinically indicated. Consider consultation with a cardiac expert as needed.

Theoretical risk of tumorigenicity as a result of vector integration

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome.

Zolgensma is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Rare instances of random vector integration into human DNA are possible with recombinant AAV. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity

Systemic corticosteroid administration and live vaccines

Live vaccines should not be administered to patients receiving high doses of corticosteroids (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent) prior to and following Zolgensma infusion (see section 8 Interactions).

Infusion-related reactions

Infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during, and/or shortly after, infusion of Zolgensma (see section 7 Adverse drug reactions). Signs and symptoms may include, but are not limited to, rash, urticaria, vomiting, dyspnea, respiratory symptoms and/or alterations in heart rate and blood pressure. Closely monitor patients and provide treatment as needed for clinical signs and symptoms of infusion-related reactions.

7 Adverse drug reactions

Summary of the safety profile

The safety of Zolgensma was evaluated in 99 patients who received Zolgensma at the recommended dose (1.1×10^{14} vg/kg) from 5 open-label clinical studies (CL-101, CL-303, CL-302, CL-304, CL-306). The patients ranged in age from 0.3 months to 7.9 months at the time of administration (weight range: 3.0 kg to 8.4 kg).

Among these 99 patients, the most frequently (≥5%) reported adverse reactions following Zolgensma administration were aspartate aminotransferase increased, alanine aminotransferase increased, transaminases increased, vomiting, thrombocytopenia, troponin increased, gamma-glutamyltransferase increased, and pyrexia.

Tabulated summary of adverse drug reactions from clinical trials

The adverse drug reactions identified with Zolgensma in patients treated with intravenous infusion at the recommended dose from the 5 open-label clinical studies are presented in Table 7-1.

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions following intravenous treatment with Zolgensma

Adverse Drug Reactions	Rate, % (N=99)	Frequency Category
Blood and lymphatic system disorders		
Thrombocytopenia[a)]	6.1	Common
Gastrointestinal disorders		
Vomiting	8.1	Common
General disorders and administration site conditions		
Pyrexia	5.1	Common
Investigations		
Aspartate aminotransferase increased	20.2	Very common
Alanine aminotransferase increased	16.2	Very common
Transaminases increased[b)]	13.1	Very common
Gamma-glutamyltransferase increased	5.1	Common
Troponin increased[c)]	5.1	Common

[a)] Thrombocytopenia includes thrombocytopenia and platelet count decreased.
[b)] Transaminases increased includes transaminases increased and hypertransaminasaemia.
[c)] Troponin increased includes troponin increased and troponin T increased.

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Zolgensma, including spontaneous case reports and literature cases. Because these reactions are reported voluntarily, it is not possible to reliably estimate their frequency which is therefore

categorized as not known. The adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from post-marketing experience (frequency not known)

Blood and lymphatic system disorders
Thrombotic microangiopathy
Hepatobiliary disorders
Acute liver failure [a)]
Acute liver injury
General disorders and administration site conditions
Infusion-related reactions [b)]
[a)] Includes fatal cases [b)] Infusion-related reactions are not under a specific system organ class and include multiple signs and symptoms that occurred during, and/or shortly after, infusion.

Description of selected adverse drug reactions

Hepatobiliary disorders

Some patients have experienced AST and ALT elevations > 20 × ULN and have been symptomatic (e.g., vomiting, jaundice), which required the use of corticosteroids, sometimes with prolonged duration and/or a higher dose (see section 6 Warnings and precautions).

Outside of clinical trials, including in the post-marketing setting, there have been reports of children developing signs and symptoms of acute liver failure (e.g., jaundice, coagulopathy, encephalopathy) typically within 2 months of treatment with Zolgensma, despite receiving prophylactic corticosteroids before and after infusion. Cases of acute liver failure with fatal outcomes have been reported.

Transient thrombocytopenia

In clinical trials, transient decreases from baseline in mean platelet counts, some of which met the criteria for thrombocytopenia, were observed at multiple time points post-dose and normally resolved within two weeks. Decreases in platelet counts were more prominent during the first week of treatment (see section 6 Warnings and precautions).

Increases in troponin-I levels

Increases in cardiac troponin-I levels up to 0.2 mcg/L following Zolgensma infusion were observed. In completed clinical studies, cardiac findings of concern have not been observed following administration of Zolgensma (see section 6 Warnings and precautions).

Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. Pre- and post-gene therapy titers of AAV9 antibody were measured in the clinical studies (see sections 6 Warnings and precautions and 12 Clinical studies).

In Zolgensma clinical trials, all patients that received Zolgensma had anti-AAV9 titers at or below 1:50 at baseline. Mean increases from baseline in anti-AAV9 titer were observed in all patients at all but 1 time-point for antibody titer levels to AAV9 peptide, reflecting normal

response to non-self viral antigen. Some patients experienced anti-AAV9 titers exceeding the level of quantification, however most of these patients did not have potentially clinically significant adverse drug reactions. Thus, no relationship has been established between high AAV9 antibody titers and the potential for adverse drug reactions or efficacy parameters.

In the AVXS-101-CL-101 clinical study, 16 patients were screened for AAV9 antibody titer: 13 had titers less than 1:50 and were enrolled in the study; three patients had titers greater than 1:50, two of whom were retested following cessation of breast-feeding and their titers were measured at less than 1:50 and both were enrolled in the study. There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for AAV9 antibodies. Patients all had less than or equal to 1:50 AAV9 antibody titer prior to treatment with Zolgensma and subsequently demonstrated an increase in AAV9 antibody titers to at least 1:102,400 and up to greater than 1:819,200. No Zolgensma-treated patient demonstrated an immune response to the transgene.

Other special populations

The safety of Zolgensma was evaluated in a post-authorization study (COAV101A12306) in 24 patients weighing ≥ 8.5 kg to ≤ 21 kg (aged approximately 1.5 to 9 years; 21 discontinued previous SMA treatment). The types of adverse reactions observed were consistent with that of the 5 open-label studies.

AST or ALT elevations > 2 × ULN were observed in the majority of patients (23/24). These patients were clinically asymptomatic and there were no elevations of bilirubin. The AST and ALT elevations were managed with the use of corticosteroids, typically with prolonged duration (mean: 218 days; range: 80-444 days) and/or a higher dose (see section 6 Warnings and precautions).

Transient decreases in platelet counts, which met the criteria for thrombocytopenia were observed in 20 out of 24 patients (see section 7 Adverse drug reactions '*Transient thrombocytopenia*').

8 Interactions

No interaction studies have been performed. Interactions with antiviral medicinal products are not expected.

Live vaccines, such as MMR and varicella, should not be administered to patients on an immunosuppressive corticosteroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent), because high doses of corticosteroids may reduce the immune response to these vaccines. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Zolgensma infusion (see section 4 Dosage regimen and administration). Seasonal RSV prophylaxis is not precluded.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 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.

9.2 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.

10 Overdosage

No data from clinical studies are available regarding overdose of Zolgensma. The dose of the Cell, Tissue and Gene Therapy Product (CTGTP) is specific to each individual patient's weight and is administered once only (see section 4 Dosage regimen and administration), therefore overdose is considered unlikely. Adjustment of the dose of prednisolone, close clinical observation and monitoring of laboratory parameters (including clinical chemistry and hematology) for systemic immune response are recommended (see section 6 Warnings and precautions).

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX09.

Mechanism of action (MOA)

Onasemnogene abeparvovec is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the monogenic root cause of spinal muscular atrophy (SMA). By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The ability of the AAV9 capsid to cross the blood brain barrier and transduce motor neurons has been demonstrated. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. Rare instances of random vector integration into human DNA are possible with recombinant AAV (see section 6 Warnings and precautions). The AAV9 virus is not known to cause disease in humans. The transgene is introduced to target cells as a self-complementary double stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken β actin hybrid), which results in

continuous and sustained SMN protein expression. Proof of the mechanism of action has been supported by non-clinical studies and by human biodistribution data.

Pharmacodynamics (PD)

There are no clinically relevant pharmacodynamics data for onasemnogene abeparvovec.

Pharmacokinetics (PK)

Onasemnogene abeparvovec vector shedding studies, which assess the amount of vector eliminated from the body through saliva, urine, feces and nasal secretions were performed.

Onasemnogene abeparvovec vector DNA was detectable in shedding samples post-infusion. Onasemnogene abeparvovec shedding was primarily via feces. Peak shedding in most patients was observed within 7 days post-dose for feces, and within 2 days post-dose for saliva, urine and nasal secretions. The majority of the vector is cleared within 30 days after dose administration.

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec 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, gonads, 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.

12 Clinical studies

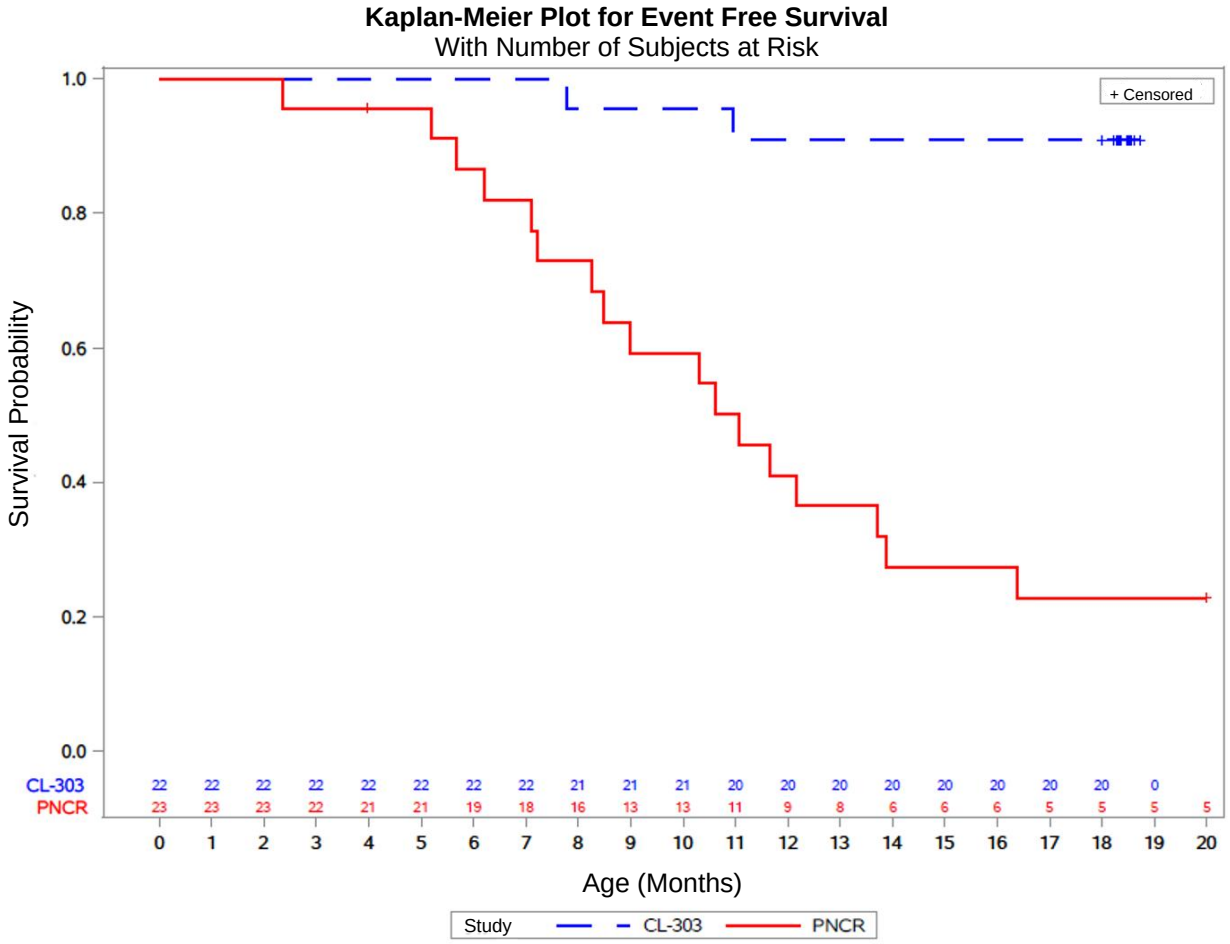
The efficacy of Zolgensma in pediatric patients with SMA with bi-allelic mutations in the *SMN1* gene was evaluated in five open-label, single-arm clinical trials.

AVXS-101-CL-303 Phase 3 Study in Patients with SMA

AVXS-101-CL-303 (Study CL-303) is a completed Phase 3, open-label, single-arm, single-dose study of intravenous administration of Zolgensma at the therapeutic dose (1.1×10^{14} vg/kg). Twenty-two patients were enrolled with Type 1 SMA and 2 copies of *SMN2*. Before treatment with Zolgensma, none of the 22 patients required non-invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., no need for non-oral nutrition). The mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score at baseline was 32.0 (range, 18 to 52). The mean age of the 22 patients at the time of treatment was 3.7 months (range, 0.5 to 5.9 months).

Of the 22 enrolled patients, 21 patients survived without permanent ventilation (i.e., event-free survival) to ≥ 10.5 months of age, 20 patients survived to ≥ 14 months of age (co-primary efficacy endpoint), and 20 patients survived event-free to 18 months of age. Three patients did not complete the study, of which two patients had an event (death or permanent ventilation) leading to 90.9% (95% CI: 79.7%, 100.0%) event-free survival (alive without permanent ventilation) at 14 months of age (see Figure 12-1).

Figure 12-1 Time (months) to death or permanent ventilation in Study CL-303



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort

For the 14 patients in Study CL-303 that achieved the milestone of independent sitting for at least 30 seconds at any visit during the study, the median age when this milestone was first demonstrated was 12.6 months (range, 9.2 to 18.6 months). Thirteen patients (59.1%) confirmed the milestone of independent sitting for at least 30 seconds at the 18 month visit (co-primary endpoint, $p<0.0001$). One patient achieved the milestone of sitting independently for 30 seconds at 16 months of age, but this milestone was not confirmed at the Month 18 visit. The video-confirmed developmental milestones for patients in Study CL-303 are summarized in Table 12-1.

Table 12-1 Median time to video documented achievement of motor milestones in Study CL-303

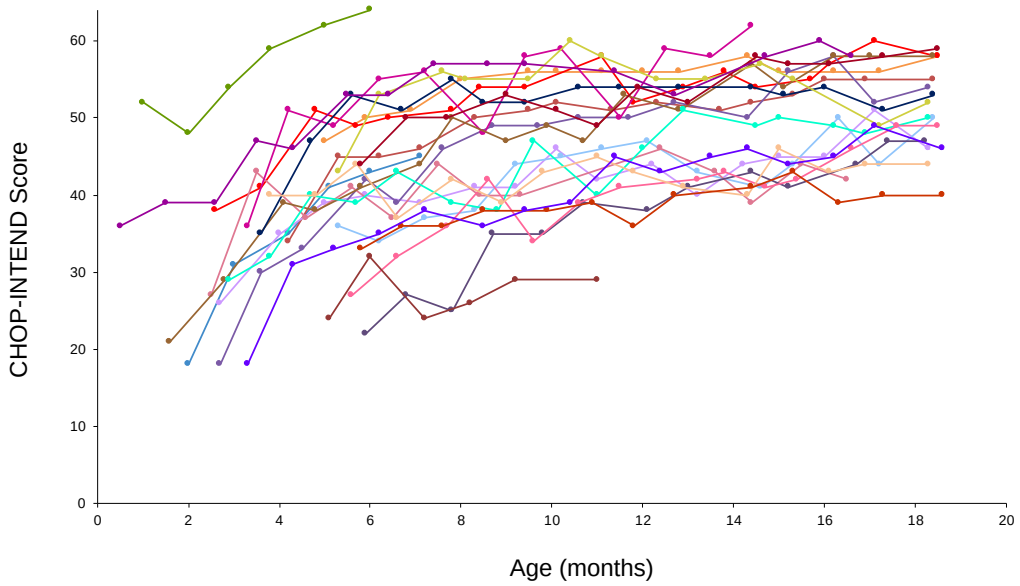
Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (Months)	95% Confidence interval
Head control	17/20* (85.0)	6.8	(4.77, 7.57)
Rolls from back to sides	13/22 (59.1)	11.5	(7.77, 14.53)
Sits without support for 30 seconds	14/22 (63.6)	12.5	(10.17, 15.20)
Sitting without support for at least 10 seconds	14/22 (63.6)	13.9	(11.00, 16.17)

*2 patients were reported to have Head Control by clinician assessment at baseline.

One patient (4.5%) could also walk with assistance at 12.9 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, 18 of the 22 patients were independent of ventilatory support at 18 months of age.

Motor function improvements were also observed as measured by CHOP-INTEND, see Figure 12-2. Twenty-one patients (95.5%) achieved a CHOP-INTEND score ≥ 40, 14 patients (63.6%) achieved a CHOP-INTEND score ≥ 50, and 9 patients (40.9%) achieved a CHOP-INTEND score ≥ 58. Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40.

Figure 12-2 CHOP-INTEND Motor Function Scores in Study CL-303 (N=22)



AVXS-101-CL-302 Phase 3 Study in Patients with SMA

AVXS-101-CL-302 (Study CL-302) is a completed Phase 3, open-label, single-arm, single-dose study of intravenous administration of Zolgensma at the therapeutic dose (1.1×10^{14} vg/kg). Thirty-three patients were enrolled with Type 1 SMA and 2 copies of *SMN2*. Before treatment with Zolgensma, 9 patients (27.3%) reported ventilatory support and 9 patients (27.3%) reported feeding support. The mean CHOP-INTEND score of the 33 patients at baseline was 27.9 (range, 14 to 55). The mean age of the 33 patients at the time of treatment was 4.1 months (range, 1.8 to 6.0 months).

Of the 33 enrolled patients (Efficacy Completers population), one patient (3%) was dosed outside of protocol age range and was therefore not included in the intent-to-treat (ITT) population. Of the 32 patients in the ITT population, one patient (3%) died during the study, due to disease progression.

Of the 32 patients in the ITT population, 14 patients (43.8%) achieved the milestone of sitting without support for at least 10 seconds at any visit up to and including the 18 month visit (primary efficacy endpoint). The median age when this milestone was first achieved was 15.9 months (range, 7.7 to 18.6 months). Thirty-one patients (96.9%) in the ITT population

survived without permanent ventilation (i.e., event-free survival) to ≥ 14 months of age (secondary efficacy endpoint, see Figure 12-3).

Figure 12-3 Time (months) to death or permanent ventilation in Study CL-302

PNCR = Pediatric Neuromuscular Clinical Research natural history cohort

The additional video-confirmed developmental milestones for patients in the Efficacy Completers population in Study CL-302 at any visit up to and including the 18 month visit are summarized in Table 12-2.

Table 12-2 Median time to video documented achievement of motor milestones in Study CL-302 (Efficacy Completers population)

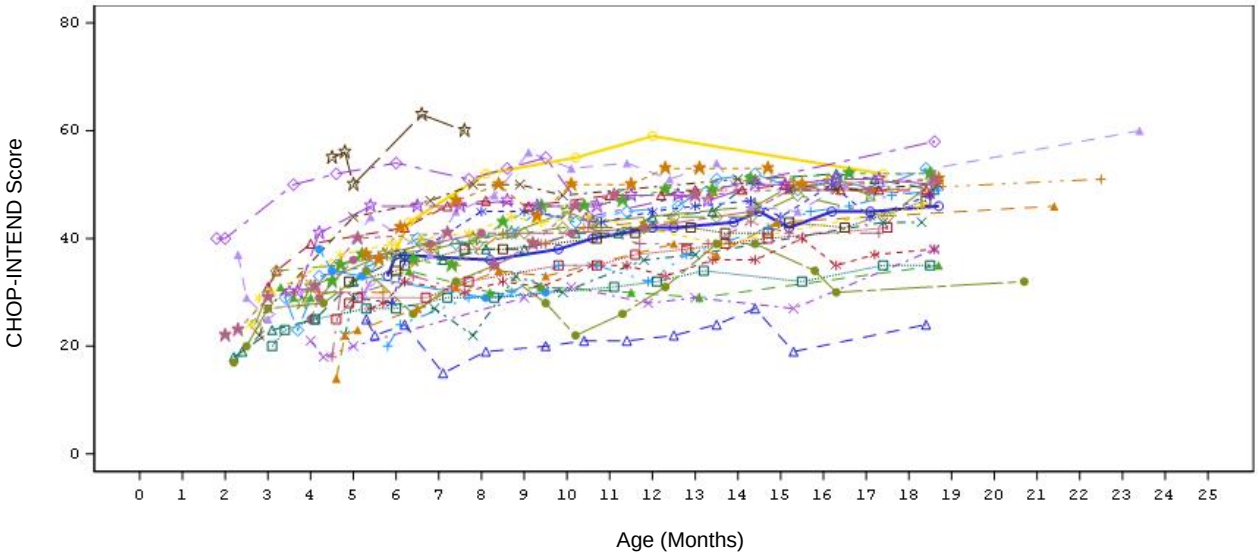
Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (Months)	95% Confidence interval
Head control	23/30* (76.7)	8.0	(5.8, 9.2)
Rolls from back to sides	19/33 (57.6)	15.3	(12.5, 17.4)
Sits without support for at least 30 seconds	16/33 (48.5)	14.3	(8.3, 18.3)

*3 patients were reported to have Head Control by clinician assessment at baseline.

One patient (3%) achieved the motor milestones of crawling, standing with assistance, stands alone, walking with assistance, and walking alone all by the age of 18 months.

Of the 33 enrolled patients, 24 patients (72.7%) achieved a CHOP-INTEND score ≥ 40, 14 patients (42.4%) achieved a CHOP-INTEND score ≥ 50, and 3 patients (9.1%) achieved a CHOP-INTEND score ≥ 58 (see Figure 12-4). Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40.

Figure 12-4 CHOP-INTEND Motor Function Scores in Study CL-302 (Efficacy Completers population; N=33)*

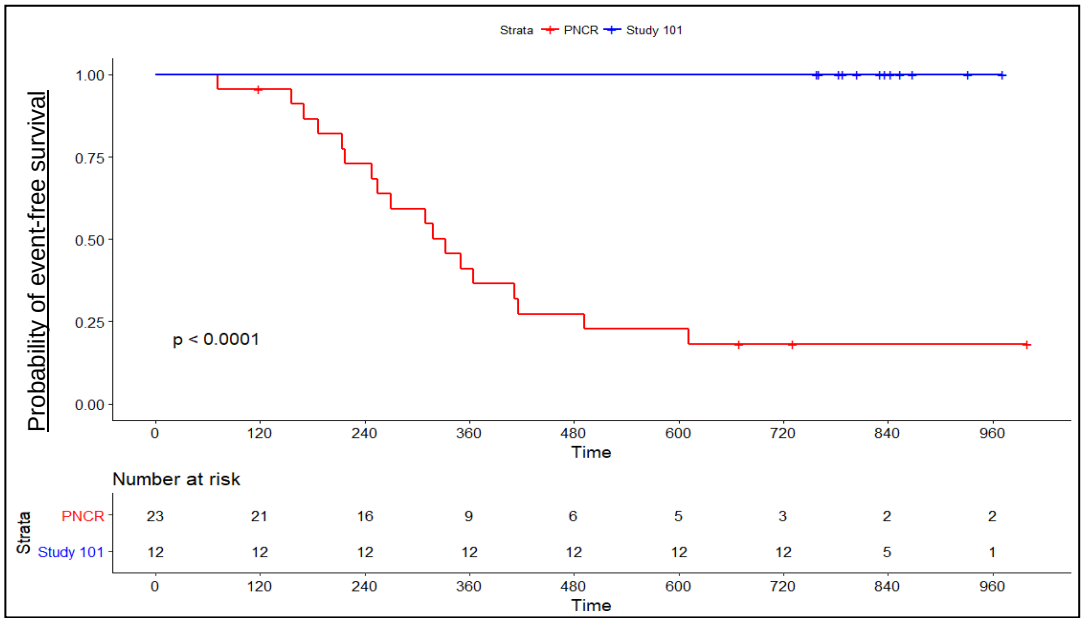


*Note: The total score programmatically calculated for one patient ( ) at Month 7 (total score=3) is considered invalid. All items were not scored and the total score should have been set to Missing (i.e. not calculated).

AVXS-101-CL-101 Phase 1 Study in Patients with SMA

The results seen in Study CL-303 are supported by completed study AVXS-101-CL-101 (Phase 1 study in Type 1 SMA, Study CL-101) in which Zolgensma was administered as a single intravenous infusion in 12 patients from 3.6 kg to 8.4 kg (0.9 to 7.9 months of age). At 14 months of age, all treated patients were event-free, i.e. survived without permanent ventilation, compared to 25% in the natural history cohort. At the end of the study (24 months post-dose), all treated patients were event-free, compared to less than 8% in the natural history cohort, see Figure 12-5.

Figure 12-5 Time (days) to death or permanent ventilation in Study CL-101



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort.

At 24 months of follow up post-dose, 10 out of 12 patients were able to sit without support for ≥ 10 seconds, 9 patients were able to sit without support for ≥ 30 seconds and 2 patients were able to stand and walk without assistance. Ten of 12 patients from Study CL-101 continue to be followed in a long-term study (for up to 6.6 years after dosing) and all 10 patients were alive and free of permanent ventilation as of 23 May 2021. All patients have either maintained previously attained milestones or gained new milestones including sitting with support, stand with assistance and walk alone. Five of the 10 patients did not report concomitant nusinersen or risdiplam treatment during the long-term study. Maintenance of efficacy and achievement of milestones can therefore not be solely attributed to Zolgensma in the other 5 patients. The milestone of standing with assistance was newly acquired by 2 patients who had not received nusinersen or risdiplam at any point prior to the time this milestone was achieved.

AVXS-101-CL-304 Phase 3 Study in Patients with pre-symptomatic SMA

Study CL-304 is a completed, global, Phase 3, open-label, single-arm, single-dose, multicenter study of intravenous Zolgensma in pre-symptomatic newborn patients up to 6 weeks of age expected to develop SMA with 2 (cohort 1, n=14) or 3 (cohort 2, n=15) copies of survival motor neuron 2 (SMN2) gene.

Cohort 1

The 14 treated patients with 2 copies of SMN2 were followed to 18 months of age. All patients survived event-free to ≥ 14 months of age without permanent ventilation.

All 14 patients achieved independent sitting for at least 30 seconds at any visit up to the 18 months of age visit (primary efficacy endpoint), at ages ranging from 5.7 to 11.8 months, with 11 of the 14 patients who achieved independent sitting at or before 279 days of age, the 99th percentile for development of this milestone. Nine patients achieved the milestone of walking alone (64.3%). All 14 patients achieved a CHOP-INTEND score ≥ 58 at any visit up to the 18 months of age visit. No patients required any ventilatory support or any feeding support during the study.

Cohort 2

The 15 treated patients with 3 copies of SMN2 were followed to 24 months of age. All patients survived event-free to 24 months of age without permanent ventilation.

All 15 patients were able to stand alone without support for at least 3 seconds (primary efficacy endpoint), at ages ranging from 9.5 to 18.3 months, with 14 of the 15 patients who achieved standing alone at or before 514 days of age, the 99th percentile for development of this milestone. Fourteen patients (93.3%) were able to walk at least five steps independently. All 15 patients achieved a scaled score of ≥ 4 on Bayley-III Gross and Fine Motor Subtests within 2 standard deviations of the mean for age at any post-baseline visit up to 24 months of age. No patients required any ventilatory support or any feeding support during the study.

COAV101A12306 Phase 3 Study in Patients with SMA weighing ≥ 8.5 kg to ≤ 21 kg

Study COAV101A12306 is a completed, Phase 3, open-label, single-arm, single-dose, multicenter study of intravenous administration of Zolgensma at the therapeutic dose (1.1×10^{14} vg/kg) in 24 pediatric patients with SMA weighing ≥ 8.5 kg to ≤ 21 kg (median weight: 15.8 kg). The patients ranged in age from approximately 1.5 to 9 years at the time of administration. One of the 24 patients was under the age of 2 at the time of administration (median age: 4.9 years). Patients had 2 to 4 copies of SMN2 (two [n=5], three [n=18], four [n=1] copies). Before treatment with Zolgensma, 21 patients discontinued their previous

treatment with nusinersen or risdiplam. At baseline, patients had a mean Hammersmith Functional Motor Scale - Expanded (HFMSE) score of 28.3 and a mean Revised Upper Limb Module (RULM) score of 22.0. In addition, all patients demonstrated the milestones of head control and sitting with support, 21 were able to sit without support, and six demonstrated the highest possible achievable milestones of standing alone and walking alone.

At Week 52, the mean change from baseline in overall HFMSE total score was 3.7 (18/24 patients). The mean increase in overall RULM total score was 2.0 (17/24 patients) at Week 52. Four patients achieved new developmental milestones. Milestones observed at the baseline visit were maintained to Week 52 for the majority of patients. Two patients who did not demonstrate previously achieved developmental milestones showed improvement in the HFMSE score from baseline to Week 52.

13 Non-clinical safety data

Following intravenous administration in neonatal mice, vector was widely distributed, with the highest vector DNA levels generally detected in the heart, liver, lungs and skeletal muscle. The expression of transgene mRNA showed similar patterns. Following intravenous administration in juvenile non-human primates, vector was widely distributed with subsequent expression of transgene mRNA, with the highest concentrations of vector DNA and transgene mRNA tending to occur in the liver, muscle, and heart. Vector DNA and transgene mRNA in both species was detected in the spinal cord, brain, and gonads.

In pivotal 3-month mouse toxicology studies, the main target organs of toxicity identified were the heart and liver. Onasemnogene abeparvovec-related findings in the ventricles of the heart were comprised of dose-related inflammation, oedema and fibrosis. In the atria of the heart, inflammation, thrombosis, myocardial degeneration/necrosis and fibroplasia were observed. A No Adverse Effect Level (NoAEL) was not identified for onasemnogene abeparvovec in mouse studies as ventricular myocardial inflammation/oedema/fibrosis and atrial inflammation were observed at the lowest dose tested (1.5×10^{14} vg/kg). This dose is regarded as the Maximum Tolerated Dose and approximately 1.4-fold the recommended clinical dose. Onasemnogene abeparvovec-related mortality was, in the majority of mice, associated with atrial thrombosis, and observed at 2.4×10^{14} vg/kg. The cause of the mortality in the rest of the animals was undetermined, although microscopic degeneration/regeneration in the hearts of these animals was found.

Liver findings in mice were comprised of hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. In long-term toxicity studies with intravenous and intrathecal (not indicated for use) administration of onasemnogene abeparvovec in juvenile non-human primates, liver findings, including single cell necrosis of hepatocytes and oval cell hyperplasia, demonstrated partial (IV) or complete (IT) reversibility.

In a 6-month toxicology study conducted in juvenile non-human primates, administration of a single dose of onasemnogene abeparvovec at the clinically recommended intravenous dose, with or without corticosteroid treatment, resulted in acute, minimal to slight mononuclear cell inflammation and neuronal degeneration in the dorsal root ganglia (DRG) and trigeminal ganglia (TG), as well as axonal degeneration and/or gliosis in the spinal cord. At 6 months, these non-progressive findings resulted in full resolution in the TG, and partial resolution (decreased incidence and/or severity) in the DRG and spinal cord. Following intrathecal

administration of onasemnogene abeparvovec (not indicated for use), these acute, non-progressive findings were noted with minimal to moderate severity in juvenile non-human primates with partial to full resolution at 12 months. These findings in non-human primates had no correlative clinical observations, therefore the clinical relevance in humans is unknown.

Genotoxicity, carcinogenicity and reproduction toxicity studies have not been conducted with onasemnogene abeparvovec.

14 Pharmaceutical information

Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

Shelf Life

- A shelf-life of 24 months at storage condition of ≤ -60°C.

Special precautions for storage

- Zolgensma is shipped and delivered frozen (≤ -60°C) in clear vials.
- Upon receipt, immediately place the kit in a refrigerator at 2°C to 8°C.
- Store in the original carton.
- Zolgensma is stable for 14 days from receipt when stored at 2°C to 8°C.
- DO NOT REFREEZE.
- Must use within 14 days of receipt.

After thawing, Zolgensma should be given as soon as possible. Once the dose volume is drawn into the syringe it must be infused within 8 hours. Discard the vector-containing syringe if not infused within the 8-hour timeframe.

Zolgensma must be kept out of the reach and sight of children.

Instructions for use and handling

Each vial is for single use only.

This Cell, Tissue and Gene Therapy Product (CTGTP) contains genetically-modified organisms. Appropriate precautions for the handling, disposal or accidental exposure of Zolgensma should be followed:

- Zolgensma should be handled aseptically under sterile conditions.
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering Zolgensma. Personnel should not work with Zolgensma if skin is cut or scratched.
- All spills of Zolgensma must be wiped with absorbent gauze pads and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of per institutional guidelines for biohazard waste.
- All materials that may have come in contact with Zolgensma (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local biosafety guidelines.

<u>Accidental exposure</u>

Accidental exposure to Zolgensma must be avoided.

In case of accidental exposure to skin, the affected area must be thoroughly cleansed with soap and water for at least 15 minutes. In case of accidental exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Special precautions for disposal

Any unused Cell, Tissue and Gene Therapy Product (CTGTP) or waste material should be disposed of in accordance with local requirements.

Temporary vector shedding of Zolgensma occurs primarily through body waste. Advise caregivers on the proper handling of patient feces:

- Good hand-hygiene is required when coming into direct contact with patient body waste for a minimum of 1 month after Zolgensma infusion.
- Disposable diapers should be sealed in disposable trash bags and discarded in regular trash.

Presentation

Onasemnogene abeparvovec is supplied in a vial (10 mL polymer crystal zenith) with stopper (20 mm chlorobutyl rubber) and seal (aluminum, flip-off) with a coloured cap (plastic), in two different vial fill volume sizes, either 5.5 mL or 8.3 mL.

The dose of onasemnogene abeparvovec and exact number of vials required for each patient is calculated according to the patient's weight (see section 4 and Table 14-1).

Table 14-1 Carton/kit configurations

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per carton
2.6 – 3.0	0	2	2
3.1 – 3.5	2	1	3
3.6 – 4.0	1	2	3
4.1 – 4.5	0	3	3
4.6 – 5.0	2	2	4
5.1 – 5.5	1	3	4
5.6 – 6.0	0	4	4
6.1 – 6.5	2	3	5
6.6 – 7.0	1	4	5
7.1 – 7.5	0	5	5
7.6 – 8.0	2	4	6
8.1 – 8.5	1	5	6
8.6 – 9.0	0	6	6
9.1 – 9.5	2	5	7
9.6 – 10.0	1	6	7
10.1 – 10.5	0	7	7
10.6 – 11.0	2	6	8
11.1 – 11.5	1	7	8
11.6 – 12.0	0	8	8

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per carton
12.1 – 12.5	2	7	9
12.6 – 13.0	1	8	9
13.1 – 13.5	0	9	9
13.6 – 14.0	2	8	10
14.1 – 14.5	1	9	10
14.6 – 15.0	0	10	10
15.1 – 15.5	2	9	11
15.6 – 16.0	1	10	11
16.1 – 16.5	0	11	11
16.6 – 17.0	2	10	12
17.1 – 17.5	1	11	12
17.6 – 18.0	0	12	12
18.1 – 18.5	2	11	13
18.6 – 19.0	1	12	13
19.1 – 19.5	0	13	13
19.6 – 20.0	2	12	14
20.1 – 20.5	1	13	14
20.6 – 21.0	0	14	14

[a] Vial nominal concentration is 2×10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL.

[b] Vial nominal concentration is 2×10^{13} vg/mL and contains an extractable volume of not less than 8.3 mL.

Manufacturer

See folding box

Date of first approval: Apr 2023

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Novartis Europharm Limited