SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolgensma 2×10^{13} vector genomes/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human 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.

2.2 Qualitative and quantitative composition

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 customised to meet dosing requirements for individual patients depending on their weight (see sections 4.2 and 6.5).

Excipient with known effect

This medicinal product contains 0.2 mmol sodium per mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear to slightly opaque, colourless to faint white solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zolgensma is indicated for the treatment of:

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

4.2 Posology and method of administration

Treatment should be initiated and administered in clinical centres and supervised by a physician experienced in the management of patients with SMA.

Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including, but not limited to:

- AAV9 antibody testing using an appropriately validated assay,
- liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, partial thromboplastin time (PTT), and international normalised ratio (INR),
- creatinine,
- complete blood count (including haemoglobin and platelet count), and

- troponin-I.

The need for close monitoring of liver function, platelet count and troponin-I after administration and the need for corticosteroid treatment are to be considered when establishing the timing of onasemnogene abeparvovec treatment (see section 4.4).

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 onasemnogene abeparvovec infusion. In case of acute or chronic uncontrolled active infections, treatment should be postponed until the infection has resolved and the patient is clinically stable (see sub-sections 4.2 'Immunomodulatory regimen' and 4.4 'Systemic immune response').

Posology

For single-dose intravenous infusion only.

Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.

Table 1 gives the recommended dosing for patients who weigh 2.6 kg to 21.0 kg.

Table 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

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

[a] NOTE: Number of vials per kit and required number of kits is weight-dependent. Dose volume is calculated using the upper limit of the patient weight range.

Immunomodulatory regimen

An immune response to the AAV9 capsid will occur after administration of onasemnogene abeparvovec (see section 4.4). This can lead to elevations in liver aminotransferases, elevations of troponin I, or decreased platelet counts (see sections 4.4 and 4.8). To dampen the immune response immunomodulation with corticosteroids is recommended. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see section 4.5).

Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for signs and symptoms of active infectious disease of any nature.

Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen following the schedule below (see Table 2). If at any time patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a paediatric gastroenterologist or hepatologist and adjustment to the recommended immunomodulatory regimen, including increased dose, longer duration or

prolongation of corticosteroid taper, should be considered (see section 4.4). If oral corticosteroid therapy is not tolerated intravenous corticosteroid may be considered as clinically indicated.

Table 2 Pre- and post-infusion immunomodulatory regimen

Pre-infusion	24 hours prior to onasemnogene abeparvovec	Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used)
Post-infusion	30 days (including the day of administration of onasemnogene abeparvovec)	Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used)
	Followed by 28 days: *For patients with unremarkable findings (normal clinical exam, total bilirubin, and whose ALT and AST values are both below 2 × upper limit of normal (ULN) at the end of the 30 days period:* **or** *For patients with liver function abnormalities at the end of the 30 days period: continuing until the AST and ALT values are below 2 × ULN and all other assessments (e.g. total bilirubin) return to normal range, followed by tapering over 28 days or longer if needed.*	Systemic corticosteroids should be tapered gradually. Tapering of prednisolone (or equivalent if another corticosteroid is used), e.g. 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day oral prednisolone Systemic corticosteroids (equivalent to oral prednisolone 1 mg/kg/day) Systemic corticosteroids should be tapered gradually.

Liver function (ALT, AST, total bilirubin) should be monitored at regular intervals for at least 3 months following onasemnogene abeparvovec infusion (weekly in the first month and during the entire corticosteroid taper period, followed by every two weeks for another month), and at other times as clinically indicated. Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly clinically assessed and monitored closely (see section 4.4).

If another corticosteroid is used by the physician in place of prednisolone, similar considerations and approach to taper the dose after 30 days should be taken as appropriate.

Special populations

Renal impairment

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

Hepatic impairment

Patients with ALT, AST, total bilirubin levels (except due to neonatal jaundice) >2 × ULN or positive serology for hepatitis B or hepatitis C have not been studied in clinical studies with onasemnogene abeparvovec. Onasemnogene abeparvovec therapy should be carefully considered in patients with hepatic impairment (see sections 4.4 and 4.8). A dose adjustment should not be considered.

0SMN1/1SMN2 genotype

No dose adjustment should be considered in patients with a bi-allelic mutation of the SMN1 gene and only one copy of SMN2 (see section 5.1).

Anti-AAV9 antibodies

No dose adjustment should be considered in patients with baseline anti-AAV9 antibody titres above 1:50 (see section 4.4).

Paediatric population

The safety and efficacy of onasemnogene abeparvovec in premature neonates before reaching full-term gestational age have not been established. No data are available. Administration of onasemnogene abeparvovec 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 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established. Currently available data are described in section 5.1. A dose adjustment should not be considered (see Table 1).

Method of administration

For intravenous use.

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. It should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus.

Insertion of a secondary (‘back-up’) catheter is recommended in case of blockage in the primary catheter. Following completion of infusion, the line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains a genetically-modified organism. Healthcare professionals should therefore take appropriate precautions (use of gloves, safety goggles, laboratory coat and sleeves) when handling or administering the product (see section 6.6).

For detailed instructions on the preparation, handling, accidental exposure and disposal (including proper handling of bodily waste) of onasemnogene abeparvovec, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Pre-existing immunity against AAV9

Anti-AAV9 antibody formation can take place after natural exposure. There have been several studies on the prevalence of AAV9 antibodies in the general population that show low rates of prior exposure to AAV9 in the paediatric population. Patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec. Re-testing may be performed if AAV9 antibody titres are reported as above 1:50. It is not yet known whether or under what conditions onasemnogene abeparvovec can be safely and effectively administered in the presence of anti-AAV9 antibodies above 1:50 (see sections 4.2 and 5.1).

Advanced SMA

Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of onasemnogene abeparvovec in symptomatic patients depends on the degree of disease burden at the time of treatment, with earlier treatment resulting in potential higher benefit. While advanced symptomatic SMA patients will not achieve the same gross motor development as unaffected healthy peers they may clinically benefit from gene replacement therapy, dependent on the advancement of disease at the time of treatment (see section 5.1).

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 onasemnogene abeparvovec in patients with advanced SMA, kept alive through permanent ventilation and without the ability to thrive, is not established.

Immunogenicity

An immune response to the AAV9 capsid and T-cell mediated immune response, will occur after infusion of onasemnogene abeparvovec, including antibody formation against the AAV9 capsid despite the immunomodulatory regimen recommended in section 4.2 (see also sub-section '*Systemic immune response*' below).

Hepatotoxicity

Immune mediated hepatotoxicity is generally manifested as elevated ALT and/or AST levels. Acute serious liver injury and acute liver failure, including fatal cases, have been reported with onasemnogene abeparvovec use, typically within 2 months after infusion and despite receiving corticosteroids before and after infusion. Immune mediated hepatotoxicity may require adjustment of the immunomodulatory regimen including longer duration, increased dose, or prolongation of the corticosteroid taper.

- The risks and benefits of onasemnogene abeparvovec therapy should be carefully considered in patients with pre-existing hepatic impairment.
- Patients with pre-existing hepatic impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury (see section 4.2).
- Administration of AAV vector often results in aminotransferase elevations.
- Acute serious liver injury and acute liver failure have occurred with onasemnogene abeparvovec. Cases of acute liver failure with fatal outcome have been reported (see section 4.8).
- Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (see section 4.2).
- In order to mitigate potential aminotransferase elevations, a systemic corticosteroid should be administered to all patients before and after onasemnogene abeparvovec infusion (see section 4.2).
- Liver function should be monitored at regular intervals for at least 3 months after infusion, and at other times as clinically indicated (see section 4.2).
- Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly clinically assessed and monitored closely.
- In case hepatic injury is suspected, prompt consultation with a paediatric gastroenterologist or hepatologist, adjustment of the recommended immunomodulatory regimen and further testing is recommended (e.g. albumin, prothrombin time, PTT, and INR).

AST/ALT/total bilirubin should be assessed weekly for the first month after onasemnogene abeparvovec infusion and during the entire corticosteroid taper period. Tapering of prednisolone should not be considered until AST/ALT levels are less than 2 × ULN and all other assessments (e.g. total bilirubin) return to normal range (see section 4.2). 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.

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in onasemnogene abeparvovec clinical studies. In most cases, the lowest platelet value occurred the first week following onasemnogene abeparvovec infusion.

Post-marketing cases with platelet count <25 x 10^9/L have been reported to occur within two weeks following administration.

Platelet counts should be obtained before onasemnogene abeparvovec infusion and should be closely monitored 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 with onasemnogene abeparvovec (see section 4.8). Cases generally occurred within the first two weeks after onasemnogene abeparvovec infusion. TMA is an acute and life-threatening condition, which is characterised by thrombocytopenia and microangiopathic haemolytic anaemia. Fatal outcomes have been reported. Acute kidney injury has also been observed. In some cases, concurrent immune system activation (e.g. infections, vaccinations) has been reported (see sections 4.2 and 4.5 for information on administration of vaccinations).

Thrombocytopenia is a key feature of TMA, therefore platelet counts should be closely monitored within the first two weeks following infusion and on a regular basis afterwards (see sub-section 'Thrombocytopenia'). In case of thrombocytopenia, further evaluation including diagnostic testing for haemolytic anaemia and renal dysfunction should be undertaken promptly. If patients show clinical signs, symptoms or laboratory findings consistent with TMA, a specialist should be consulted immediately to manage TMA as clinically indicated. Caregivers should be informed about signs and symptoms of TMA and should be advised to seek urgent medical care if such symptoms occur.

Elevated troponin-I

Increases in cardiac troponin-I levels following infusion with onasemnogene abeparvovec were observed (see section 4.8). 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 onasemnogene abeparvovec infusion and monitored for at least 3 months following onasemnogene abeparvovec infusion or until levels return to within normal reference range for SMA patients. Consider consultation with a cardiac expert as needed.

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 onasemnogene abeparvovec infusion. Treatment should not be initiated concurrently to active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B), until the infection has resolved and the patient is clinically stable (see sections 4.2 and 4.4).

The immunomodulatory regimen (see section 4.2) might also impact the immune response to infections (e.g. respiratory), potentially resulting in more severe clinical courses of the infection. Patients with infection were excluded from participation in clinical trials with onasemnogene abeparvovec. Increased vigilance in the prevention, monitoring, and management of infection is recommended before and after onasemnogene abeparvovec infusion. Seasonal prophylactic treatments, that prevent respiratory syncytial virus (RSV) infections, are recommended and should be up to date. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see section 4.5).

If the duration of corticosteroid treatment is prolonged or the dose is increased, the treating physician should be aware of the possibility of adrenal insufficiency.

Risk of tumourigenicity as a result of vector integration

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

Onasemnogene abeparvovec 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 tumourigenicity.

So far, no cases of malignancies associated with onasemnogene abeparvovec treatment have been reported. In the event of a tumour, the marketing authorisation holder should be contacted for guidance on collecting patient samples for testing.

Shedding

Temporary onasemnogene abeparvovec shedding occurs, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient stools:

- Good hand-hygiene is required when coming into direct contact with patient bodily waste for a minimum of 1 month after onasemnogene abeparvovec treatment.
- Disposable nappies can be sealed in double plastic bags and disposed of in household waste.

Blood, organ, tissue and cell donation
Patients treated with Zolgensma should not donate blood, organs, tissues or cells for transplantation.

Sodium content

This medicinal product contains 4.6 mg sodium per mL, equivalent to 0.23% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each 5.5 mL vial contains 25.3 mg sodium, and each 8.3 mL vial contains 38.2 mg sodium.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Experience with use of onasemnogene abeparvovec in patients receiving hepatotoxic medicinal products or using hepatotoxic substances is limited. Safety of onasemnogene abeparvovec in these patients have not been established.

Experience with use of concomittant 5q SMA targeting agents is limited.

Vaccinations

Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see sections 4.2 and 4.4). Seasonal RSV prophylaxis is recommended (see section 4.4). Live vaccines, such as MMR and varicella, should not be administered to patients on an immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisolone or equivalent).

4.6 Fertility, Pregnancy and lactation

Human data on use during pregnancy or lactation are not available and animal fertility or reproduction studies have not been performed.

4.7 Effects on ability to drive and use machines

Onasemnogene abeparvovec has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of onasemnogene abeparvovec was evaluated in 99 patients who received onasemnogene abeparvovec at the recommended dose (1.1×10^{14} vg/kg) in 5 open-label clinical studies. The most frequently reported adverse reactions following administration were hepatic enzyme increased (24.2%), hepatotoxicity (9.1%), vomiting (8.1%), thrombocytopenia (6.1%), troponin increased (5.1%), and pyrexia (5.1%) (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions identified with onasemnogene abeparvovec in all patients treated with intravenous infusion at the recommended dose with a causal association to treatment are presented in Table 3. Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Tabulated list of adverse reactions to onasemnogene abeparvovec

Adverse Reactions by MedDRA SOC/PT and Frequency	
Blood and lymphatic system disorders	
Common	Thrombocytopenia[1)]
Not known	Thrombotic microangiopathy[2)3)]
Gastrointestinal disorders	
Common	Vomiting
Hepatobiliary disorders	
Common	Hepatotoxicity[4)]
Not known	Acute liver failure[2)3)]
Not known	Acute liver injury[2)]

General disorders and administration site conditions	
Common	Pyrexia
Investigations	
Very common	Hepatic enzyme increased[5)]
Common	Troponin increased[6)]

[1)]Thrombocytopenia includes thrombocytopenia and platelet count decreased.
[2)]Treatment-related adverse reactions reported outside of pre-marketing clinical studies, including in the post-marketing setting.
[3)]Includes fatal cases.
[4)]Hepatotoxicity includes hepatic steatosis and hypertransaminasaemia.
[5)]Hepatic enzyme increased includes: alanine aminotransferase increased, ammonia increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased and transaminases increased.
[6)]Troponin increased includes troponin increased, troponin-T increased, and troponin-I increased (reported outside of clinical studies, including in the post-marketing setting).

Description of selected adverse reactions

Hepatobiliary disorders

In clinical studies, elevated transaminases > 2 × ULN (and in some cases > 20 × ULN) were observed in 31% of patients treated at the recommended dose. These patients were clinically asymptomatic and none of them had clinically significant elevations of bilirubin. Serum transaminase elevations usually resolved with prednisolone treatment and patients recovered without clinical sequelae (see sections 4.2 and 4.4).

Outside of clinical studies, 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 onasemnogene abeparvovec, despite receiving corticosteroids before and after infusion. Cases of acute liver failure with fatal outcome have been reported.

Transient thrombocytopenia

In clinical studies-, transient decreases from baseline in mean platelet counts, some of which met the criteria for thrombocytopenia (6.1%), 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 4.4). Post-marketing cases with transient decrease in platelet count to levels $<25 \times 10^9$/L within two weeks of administration have been reported (see section 4.4).

Increases in troponin-I levels

Increases in cardiac troponin-I levels up to 0.2 mcg/L following onasemnogene abeparvovec infusion were observed. In the clinical study program, there were no clinically apparent cardiac findings observed following administration of onasemnogene abeparvovec (see section 4.4).

Immunogenicity

Pre- and post-gene therapy titres of anti-AAV9 antibodies were measured in the clinical studies (see section 4.4). All patients that received onasemnogene abeparvovec had anti-AAV9 titres at or below 1:50 before treatment. Mean increases from baseline in AAV9 titre were observed in all patients at all but 1 time-point for antibody titre levels to AAV9 peptide, reflecting normal response to non-self viral antigen. Some patients experienced AAV9 titres exceeding the level of quantification, however most of these patients did not have potentially clinically significant adverse reactions. Thus, no relationship has been established between high anti-AAV9 antibody titres and the potential for adverse reactions or efficacy parameters.

In the AVXS-101-CL-101 clinical study, 16 patients were screened for anti-AAV9 antibody titre: 13 had titres less than 1:50 and were enrolled in the study; three patients had titres greater than 1:50, two of whom were retested following cessation of breast-feeding and their titres 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 anti-AAV9 antibodies. Patients all had less than or equal to 1:50 AAV9 antibody titre prior to treatment with onasemnogene abeparvovec and subsequently demonstrated an increase in anti-AAV9 antibody titres to at least 1:102,400 and up to greater than 1:819,200.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralising 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.

No onasemnogene abeparvovec-treated patient demonstrated an immune response to the transgene.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No data from clinical studies are available regarding overdose of onasemnogene abeparvovec. Adjustment of the dose of prednisolone, close clinical observation and monitoring of laboratory parameters (including clinical chemistry and haematology) for systemic immune response are recommended (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 the disease. 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. 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.

Clinical efficacy and safety

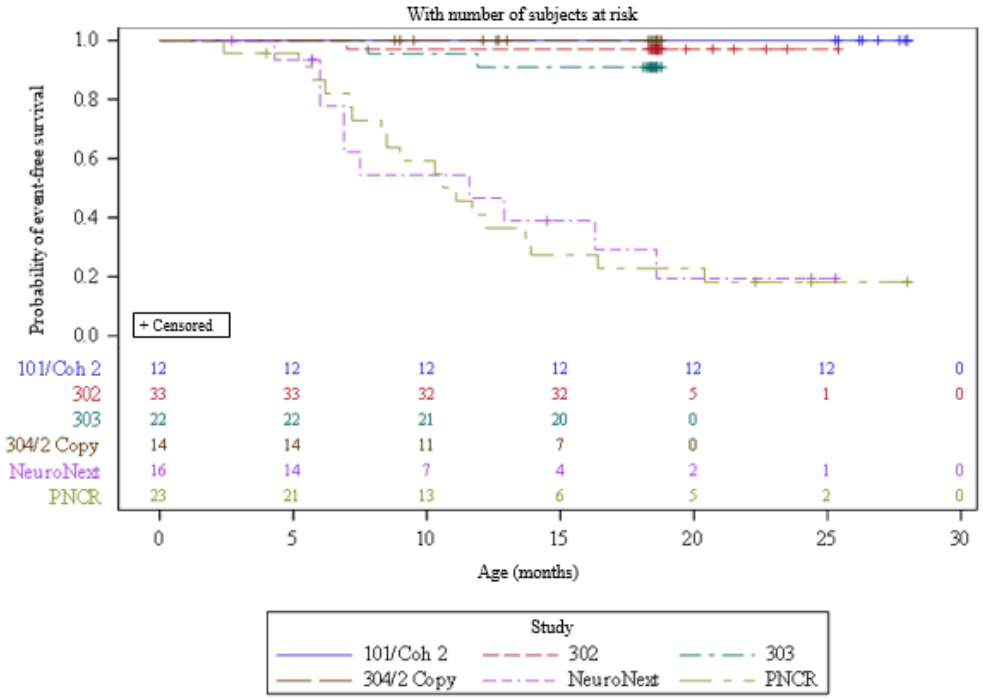
AVXS-101-CL-303 Phase 3 study in patients with Type 1 SMA

AVXS-101-CL-303 (Study CL-303) is a Phase 3 open-label, single-arm, single-dose study of intravenous administration of onasemnogene abeparvovec 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 onasemnogene abeparvovec, none of the 22 patients required non-invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., did not need 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 (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 2 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 1.

Figure 1 **Time (months) to death or permanent ventilation pooled from onasemnogene abeparvovec IV studies (CL-101, CL-302, CL-303, CL-304-2 copy cohort)**



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort

NeuroNext = Network for Excellence in Neuroscience Clinical Trials 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 summarised in Table 4. Three patients did not achieve any motor milestones (13.6%) and another 3 patients (13.6%) achieved head control as the maximum motor milestone before the 18 months of age final study visit.

Table 4 **Median time to video documented achievement of motor milestones Study CL-303**

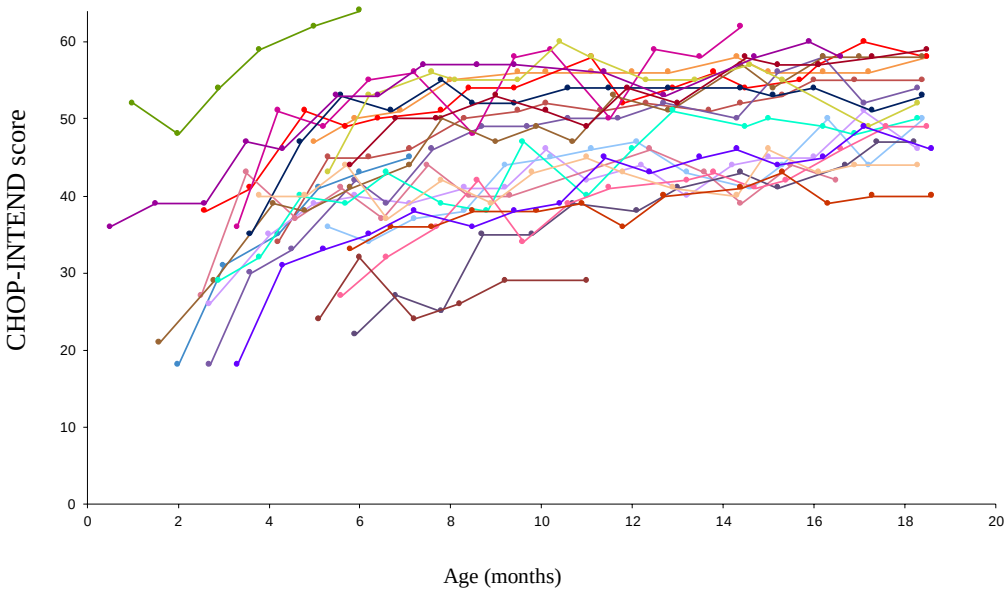
Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (months)	95% Confidence interval
Head control	17/20* (85.0)	6.8	(4.77, 7.57)
Rolls from back to sides	13/22 (59.1)	11.5	(7.77, 14.53)
Sits without support for 30 seconds (Bayley)	14/22 (63.6)	12.5	(10.17, 15.20)
Sitting without support for at least 10 seconds (WHO)	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. 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 the CHOP-INTEND, see Figure 2. Twenty-one patients (95.5%) achieved a CHOP-INTEND score ≥ 40, 14 patients (63.6%) had achieved a CHOP-INTEND score ≥ 50, and 9 patients (40.9%) had achieved a CHOP-INTEND score ≥ 58. Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40. Motor milestone achievement was observed in some patients despite plateauing of CHOP-INTEND. No clear correlation was observed between CHOP-INTEND scores and motor milestone achievement.

Figure 2 CHOP-INTEND motor function scores - Study CL-303 (N=22)



AVXS-101-CL-302 Phase 3 study in patients with Type 1 SMA

AVXS-101-CL-302 (Study CL-302) is a Phase 3, open-label, single-arm, single-dose study of intravenous administration of onasemnogene abeparvovec 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 onasemnogene abeparvovec, 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).

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 summarised in Table 5.

Table 5 Median time to video documented achievement of motor milestones in Study CL-302 (Efficacy Completers population)

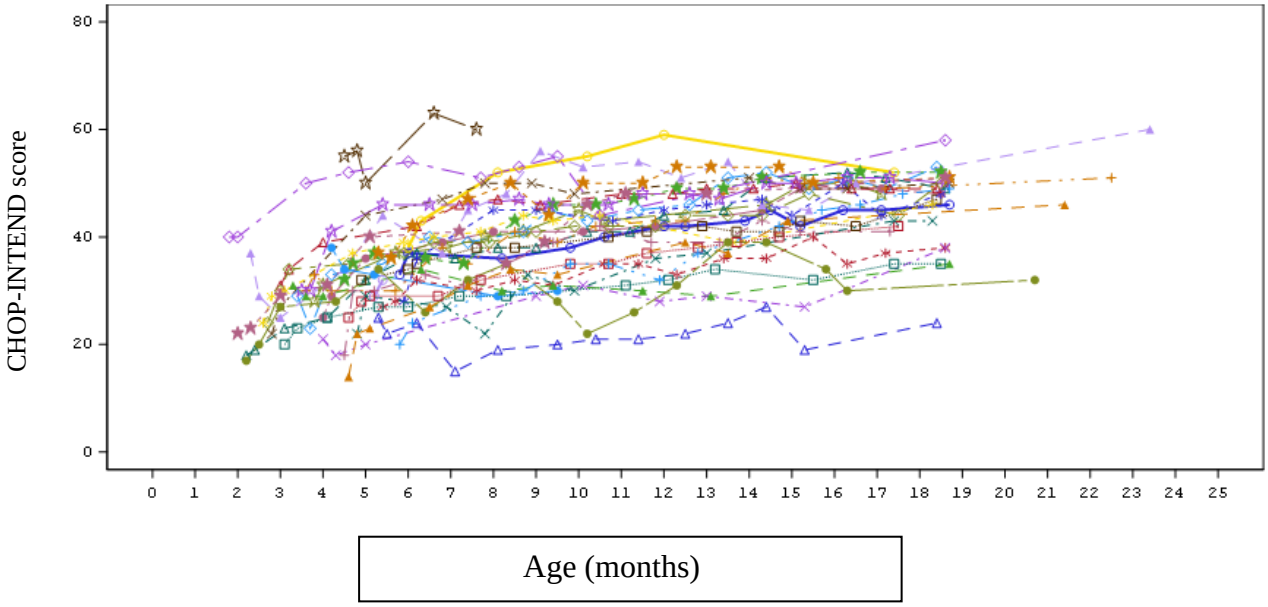
Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (months)	95% Confidence interval
Head control	23/30* (76.7)	8.0	(5.8, 9.2)
Rolls from back to sides	19/33 (57.6)	15.3	(12.5, 17.4)
Sits without support for at least 30 seconds	16/33 (48.5)	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 3). Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40.

Figure 3 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 Type 1 SMA

The results seen in Study CL-303 are supported by study AVXS-101-CL-101 (Study CL-101) a phase 1 study in patients with Type 1 SMA, in which onasemnogene abeparvovec 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, see Figure 1.

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. One out of 12 patients did not achieve head control as the maximum motor milestone before the age of 24 months. 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 such as sitting with support, standing with assistance and walking alone. Five of the 10 patients received concomitant nusinersen or risdiplam treatment at some point during the long-term study. Maintenance of efficacy and achievement of milestones can therefore not be solely attributed to onasemnogene abeparvovec in all 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 global, Phase 3, open-label, single-arm, single-dose study of intravenous administration of onasemnogene abeparvovec in pre-symptomatic newborn patients up to 6 weeks of age with 2 (cohort 1, n=14) or 3 (cohort 2, n=15) copies of *SMN2*.

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.

Onasemnogene abeparvovec has not been studied in patients with a bi-allelic mutation of the SMN1 gene and only one copy of SMN2 in clinical studies.

The licensing authority has deferred the obligation to submit the results of studies with onasemnogene abeparvovec in one or more subsets of the paediatric population in spinal muscular atrophy for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Onasemnogene abeparvovec was detectable in shedding samples post-infusion. Clearance of onasemnogene abeparvovec was primarily via faeces and the majority is cleared within 30 days after dose administration.

Biodistribution was evaluated in 2 patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec at the dose of 1.1 x 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.

5.3 Preclinical 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tromethamine

Magnesium chloride

Sodium chloride

Poloxamer 188

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months

After thawing

Once thawed, the medicinal product should not be re-frozen and may be stored refrigerated at 2°C to 8°C in the original carton for 14 days.

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.

6.4 Special precautions for storage

Store and transport frozen (≤ -60°C).

Store in a refrigerator (2°C to 8°C) immediately upon receipt.

Store in the original carton.

For storage conditions after thawing of the medicinal product, see section 6.3.

The date of receipt should be marked on the original carton before the product is stored in the refrigerator.

6.5 Nature and contents of container

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 4.2 and Table 5 below).

Table 5 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
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 × 1013 vg/mL and contains an extractable volume of not less than 5.5 mL.

[b] Vial nominal concentration is 2 × 1013 vg/mL and contains an extractable volume of not less than 8.3 mL.

6.6 Special precautions for disposal

Receipt and thawing vials

- Vials will be transported frozen (≤ -60ºC). Upon receipt vials should be refrigerated at 2°C to 8°C immediately, and in the original carton. Onasemnogene abeparvovec therapy should be initiated within 14 days of receipt of vials.
- Vials must be thawed before use. Do not use onasemnogene abeparvovec unless thawed.
- For packaging configurations containing up to 9 vials, product will be thawed after approximately 12 hours in the refrigerator. For packaging configurations containing up to 14 vials, product will be thawed after approximately 16 hours in the refrigerator. Alternatively, and for immediate use, thawing may be performed at room temperature.
- For packaging configurations containing up to 9 vials, thawing will occur from frozen state after approximately 4 hours at room temperature (20°C to 25°C). For packaging configurations containing up to 14 vials, thawing will occur from frozen state after approximately 6 hours at room temperature (20°C to 25°C)
- Before drawing the dose volume into the syringe, gently swirl the thawed product. Do NOT shake.
- Do not use this medicine if you notice any particles or discolouration once the frozen product has thawed and prior to administration.
- Once thawed, the medicinal product should not be re-frozen.
- After thawing, onasemnogene abeparvovec 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.

Administration of onasemnogene abeparvovec to the patient

To administer onasemnogene abeparvovec, draw the entire dose volume into the syringe. Remove any air in the syringe before intravenous infusion through a venous catheter.

Precautions to be taken for the handling, disposal and accidental exposure to the medicinal product

This medicinal product contains genetically-modified organisms. Appropriate precautions for the handling, disposal or accidental exposure of onasemnogene abeparvovec should be followed:

- The onasemnogene abeparvovec syringe should be handled aseptically under sterile conditions.
- Personal protective equipment (to include gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering onasemnogene abeparvovec. Personnel should not work with onasemnogene abeparvovec if skin is cut or scratched.
- All spills of onasemnogene abeparvovec must be wiped with absorbent gauze pad 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 local guidelines for handling of biological waste.
- Any unused medicinal product or waste material should be disposed of in accordance with local guidelines on handling of biological waste.
- All materials that may have come in contact with onasemnogene abeparvovec (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local guidelines on handling of biological waste.
- Accidental exposure to onasemnogene abeparvovec must be avoided. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Shedding

Temporary onasemnogene abeparvovec shedding may occur, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient bodily fluids and waste:

- Good hand-hygiene (wearing protective gloves and washing hands thoroughly afterwards with soap and warm running water, or an alcohol-based hand sanitiser) is required when coming into direct contact with patient bodily fluids and waste for a minimum of 1 month after onasemnogene abeparvovec treatment.
- Disposable nappies should be sealed in double plastic bags and can be disposed of in household waste.

7 MARKETING AUTHORISATION HOLDER

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