Date: 9 October 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Zolgensma

International non-proprietary name: onasemnogene abeparvovec

Pharmaceutical form: solution for infusion

Dosage strength(s): each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg)

Route(s) of administration: intravenous infusion

Marketing authorisation holder: Novartis Pharma Schweiz AG

Marketing authorisation no.: 67529

Decision and decision date: approved on 28.06.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AAV9	Adeno-Associated Virus Serotype 9
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
RULM	Revised Upper Limb Module
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMAIS	SMA Independence Scale
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)

TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Vg	Vector genomes

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for the active substance onasemnogene abeparvovec (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) of the medicinal product mentioned above.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 22 August 2019.

Temporary authorisation for human medicinal products
The applicant has not requested a temporary authorisation in accordance with Article 9a TPA. However, based on the submitted clinical data material and the results of the evaluation, Swissmedic granted a temporary authorisation in accordance with Art. 9a TPA

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

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.

Therapy may only be administered up to the age of 2 years.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by the patient's body weight.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	28 May 2020

Formal control completed	1 June 2020
List of Questions (LoQ)	5 August 2020
Response to LoQ	2 November 2020
Preliminary decision	5 May 2021
Response to preliminary decision	8 June 2021
Final decision	28 June 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Spinal muscular atrophy (SMA) is an autosomal recessive disease in which a loss or mutation in the survival motor neuron 1 gene (SMN1 gene) on chromosome 5q13 leads to reduced SMN protein levels. Survival motor neuron (SMN) protein deficiency causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 infantile-onset SMA is fatal, usually by 2 years of age, due to respiratory failure and infection.

There are multiple types of SMA (0-4), as shown in the following listing. The age of onset, maximum function achieved, and prognosis are primarily determined by the number of copies of the survival motor neuron 2 gene (SMN2) and correspondingly increasing amounts of SMN protein. In general, the severity of symptoms decreases and the age of onset is delayed with increasing survival motor neuron 2 gene (SMN2) copy number and correspondingly increasing amounts of SMN protein, although different patients with the same SMN2 copy number can have different clinical phenotypes.

Classification into SMA types has historically been based on the age of symptom onset and the maximum motor abilities achieved.

Classification of Spinal Muscular Atrophy

Type	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	SMN copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	-	-
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy<2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of SMN2 in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2.1 to 2.9	Three copies of SMN2 in>80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of SMN2 in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	-	Four or more copies of SMN2

Source: according to Mercuri et al. 2012, Lancet Neurol 2012; 11: 443–52

Approved treatments for SMA in Switzerland:
Approved treatments for SMA in Switzerland are Spinraza® (nusinersen) and Evrysdi® (risdiplam). According to the publicly available information (for details see www.swissmedicinfo.ch), Spinraza is an antisense oligonucleotide (ASO) for intrathecal injection, indicated for the treatment of 5q-associated spinal muscular atrophy (SMA). Evrysdi, dispensed as an oral solution, is a splicing modifier of SMN2 pre-mRNA (survival of motor neuron 2) for the treatment of 5q-associated spinal muscular atrophy (SMA) in patients 2 months of age and older.

4 Quality aspects

4.1 Drug substance

INN: onasemnogene abeparvovec

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.

Physico-chemical properties: clear to slightly opaque, colourless to faint white solution.

Manufacture:
The manufacturing process of onasemnogene abeparvovec is a complex process involving several steps of upstream and downstream manufacturing.
In the upstream process, 1 vial of the human embryonic kidney cells (HEK293) working cell bank is thawed, expanded, and transfected with a solution containing 3 DNA plasmids that contain the genetic information to produce the vector in the cells. Subsequently, the clarified harvest, containing the desired vector, is collected. In the following downstream process, further purification and filtration steps are conducted, followed by the filling of the active substance into primary containers.
The process was sufficiently validated, is described in satisfactory detail, and appropriate controls are conducted.

Specification:
In order to ensure a consistent quality of the drug substance, the specifications are sufficiently justified based on manufacturing and clinical experience, and include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and validated.

Stability:
Appropriate stability data have been presented, resulting in a suitable retest period when stored at< -60°C in appropriate primary containers.

4.2 Drug product

Description and composition:
The drug product is a single-dose, preservative-free, sterile, clear to slightly opaque, and colourless to faint white intravenous infusion of non-replicating, self-complementary AAV9 vector at a target concentration of 2.0×10^{13} vector genomes/mL. The final administered dose is based on the patient's weight.
Zolgensma solution contains tromethamine (tris), magnesium chloride, sodium chloride, and poloxamer 188 in water for injection (WFI). All excipients are of compendial quality. The pH range of the solution is 7.7 to 8.3.

Pharmaceutical development:
Sufficient description and detailed justification of the selection of excipients was provided.

Manufacture:
The drug product manufacturing process consists of thawing and pooling of the drug substance, sterile filtration and concentration adjustment, filling, visual inspection, labelling, and packaging.
The manufacturing process is described in sufficient detail including a flow diagram and narrative of each step and is considered adequate. The process is sufficiently validated, and appropriate in-process controls are performed.

Specification:
For the control of the finished product, adequate tests and acceptance criteria have been established for release and shelf-life. The specifications include relevant physico-chemical characteristics, identification, assay, potency, and purity tests, as well as safety-relevant tests.
The test methods applied are adequately validated according to recommendations of the current scientific guidelines.

Container closure system:
10 mL crystal zenith vials with a nominal fill volume of 5.5 mL or 8.3 mL are used.

Stability:
A shelf life at ≤ -60°C was established based on adequate data. As stated in the Swiss SmPC (Information for healthcare professionals), the DP should be stored and transported at ≤ -60°C, and should be stored in a refrigerator (2 - 8°C) immediately upon receipt. For detailed storage and handling instructions, the latest version of the Swiss SmPC should be consulted.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Spinal muscular atrophy (SMA) is an autosomal recessive disorder affecting newborns and children, often with lethal outcome, depending on the SMA type. The cause of SMA is the bi-allelic deletion/inactivation of the “survival motor neuron” (SMN1) gene on chromosome 5q13 resulting in the absence of SMN1 protein. In humans, there is a second SMN gene (SMN2) on chromosome 5 in multiple copies. The SMN2 gene is identical to the SMN1 gene with the exception of a C to T transition at position 6 in exon 7 resulting in a splicing defect during mRNA processing. Only 10-15% of the SMN2 transcripts result in a functional SMN2 protein. All types of SMA are linked to insufficient levels of the SMN protein and, as a consequence, to the loss of motor neurons. The function of the SMN protein is not fully understood. It is thought that it plays an important role as a chaperone in the assembly of small nuclear ribonucleoproteins that are essential for splicing of pre-mRNA molecules.

Zolgensma (onasemnogene abeparvovec, scAAV9-SMN1) is a recombinant, replication-deficient, self-complementary adeno-associated viral vector of the seroptype 9 (scAAV9), expressing the human full length SMN1 gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter. The scAAV9 viral vector is able to cross the blood-brain-barrier (BBB) after intravenous injection. Onasemnogene abeparvovec is formulated as a solution for intravenous (IV) infusion. The recommended human therapeutic dose consists of 1.1×10^{14} vector genomes (vg)/kg.

The nonclinical proof-of-concept (PoC)/efficacy and viral vector biodistribution evaluations were mainly performed in an SMA mouse model (SMNΔ7 mice) and in an inducible SMA pig model. The SMNΔ7 mouse was generated from the FVB mouse strain. It is a triple-mutant mouse with 1 mouse smn gene deleted (*smn*$1^{+/-}$) and harbouring 2 transgenic alleles (the entire human smn2 gene and a human smn2 cDNA sequence lacking the exon 7 (smnΔ7). The *smn*$1^{+/-}$ / smn2 / smnΔ7 mice are viable and can be crossed to generate offspring that are knocked out for the mouse *smn*1 gene (*smn*$1^{-/-}$ / smn2 / smnΔ7). These *smn*$1^{-/-}$ / smn2 / smnΔ7 mice (here called SMNΔ7 mice) exhibit symptoms and a neuropathology similar to SMA patients. At birth, these triple mutants are smaller than normal littermates. By Day 5, signs of muscle weakness are apparent and become progressively more pronounced over the following week as the mice display an abnormal gait, shakiness in the hind limbs, and a tendency to fall over. The mean survival of the SMNΔ7 mice is about 18 days.

A single IV treatment of SMNΔ7 mice with scAAV9-SMN1 at various times after birth showed that treatment at postnatal Day 1 or 2 resulted in a prolongation of survival. Treatment of SMNΔ7 mice at PND5 resulted only in a modest increase in the survival time, and treatment at PND10 resulted in no survival benefit. The determination of the minimum effective dose level was hampered by the fact that research-grade scAAV9-SMN1 batches were used in which the viral vector dose was not determined by a validated method. Based on retrospective re-analysis of the administered doses by a validated method, the applicant determined the minimum effective dose in SMNΔ7 mice as 1.1×10^{14} vg/kg, which also is the proposed human dose. A paper documenting the proof of concept and published in Nature Biotechnology was later retracted due to data integrity findings.

In an additional supportive study, the efficacy of scAAV9-SMN1 was also shown in an induced SMA model in juvenile pigs. In this SMA animal model, endogenous expression of SMN mRNA was reduced by postnatal intrathecal injection of an scAAV9 viral vector encoding a small hairpin RNA (shRNA) SMN construct (scAAV9-shRNA) and the therapeutic effects of intrathecal injection of scAAV9-SMN1 were evaluated. Pigs that received scAAV9-shRNA had reduced porcine SMN proteins in motor neurons and developed typical signs of SMA, including reduced electrophysiological compound muscle action potential. The phenotype of the induced SMA disease was completely prevented by 0.65×10^{13} vg/kg scAAV9-SMN1 at PND7 and substantially ameliorated when the vector was administered at PND30.

With respect to secondary pharmacodynamics, the role of SMN protein in cardiac function was investigated. In untreated SMNΔ7 mice smaller hearts and decreased left ventricle mass associated with significantly thinner ventricular walls and decreased heart rate were observed. In SMNΔ7 mice a cardiomyopathy develops by PND14. IV treatment of SMNΔ7 mice with scAAV9-SMN1 at PND1 partially reversed these abnormalities.

No specific safety pharmacology studies were performed with scAAV9-SMN1. Supporting data with respect to CNS and cardiovascular effects were provided in the mouse efficacy studies.

5.2 Pharmacokinetics

The pharmacokinetics evaluation was largely limited to the biodistribution of the scAAV9 viral vector in mice and cynomolgus monkeys (NHP) and the expression of the therapeutic SMN1 gene or a green fluorescent protein (GFP) marker gene after a single IV scAAV9 injection at different dose levels. Viral vector biodistribution analysis was evaluated as part of exploratory studies and in the context of GLP toxicology studies as non-GLP substudies.

The ability of scAAV9 to cross the BBB was assessed in an exploratory study in newborn and adult C57BL/6 mice following IV administration of an scAAV9 viral vector harbouring a GFP encoding gene under the control of the CMV-chicken β-actin hybrid promoter (scAAV9.CB.GFP). In neonatal mice, administration of 4×10^{11} vg scAAV9.CB.GFP on PND1 or PND2 resulted in predominantly neuronal transduction (>56%), with over 70% of motor neurons targeted throughout the spinal cord and in dorsal root ganglia (DRG). GFP expression was also found in cardiac and skeletal muscle. In contrast, administration of 4×10^{11}, 8×10^{11}, and 4×10^{12} vg scAAV9.CB.GFP to adult (~70 days old) mice resulted in transduction of mainly glial cells, with only 5−10% transduced neurons. Thus, the scAAV9 viral vector is able to cross the BBB following IV administration in mice, allowing the delivery of genes to the CNS, with high transduction rates of neurons in newborn animals.

In SMNΔ7 mice, the reconstitution of SMN1 protein expression was also evaluated after IV injection at PND1 of 5×10^{11} vg scAAV9-SMN1. In scAAV-9-SMN1-treated mice, SMN protein levels were increased in the brain, the spinal cord, and the muscles compared to untreated SMNΔ7 mice. The SMN protein levels remained lower than those observed in wild-type control animals.

Biodistribution of scAAV9-SMN1 was further analysed in wild-type FVB mice in the context of two 12-week and one 24-week toxicology studies.
In the first 12-week toxicology study, the biodistribution of scAAV9-SMN1 was studied following a single IV administration in neonatal FVB mice at PND1 using a product manufactured by the commercial process and characterised by validated methods. The administered dose was 2.37×10^{14} vg/kg. The scAAV9-SMN1 viral vector was quantified in DNA isolated from 7 organs at 3, 7, and 12 weeks post-injection. Vector DNA was detected in the brain and spinal cord at significant levels, indicating that the vector was able to cross the BBB. High levels of vector DNA were observed at all assessed time points. The highest vector genome levels were found in the heart, lung, liver, and skeletal muscle. In the spleen, lower levels were observed. The distribution of scAAV9-SMN1 into gonads was not evaluated. The presence of scAAV9.CB.SMN genomes in the cells of tissues resulted in SMN gene expression, as evidenced by ddPCR specific for the cDNA generated from mRNA extracted from the same tissues as for genomic DNA.

In the second 12-week toxicology study, 3 different viral vector doses manufactured according to the commercial process were tested (1.5×10^{14}, 2.4×10^{14}, and 3×10^{14} vg/kg). The scAAV9-SMN1 viral vector biodistribution and the SMN1 expression were analysed in 9 tissues, confirming the results of the first study. In the second study, testes and ovary were included and viral vector distribution and SMN1 expression was shown in gonadal tissues.

In the 24-week toxicology study, the scAAV9-SMN1 viral vector was not manufactured according to the commercial process and the biodistribution was characterised with unvalidated analytical methods. Expression of SMN1 mRNA was determined in various organs by a qualified qPCR method. Viral vector DNA were detected in all tissues, indicating systemic exposure. Specifically, high levels of vector DNA were detected in the heart, liver, lung, lymph nodes, masseter muscle (injection site), quadriceps muscle, and spinal cord. The viral vector levels remained high at all time points, indicating persistence. Lower levels of viral vector DNA were detected in the jejunum, kidney, pancreas, and spleen from all treated groups. The lowest levels were detected in gonadal samples. SMN1 expression was quantified in RNA samples isolated from 11 different tissues. In contrast to the 12-week study, the gonads were the only tissue with no detectable SMN1 expression. As in the second 12-week study SMN1 expression was shown in gonads, gonadal expression of SMN1 protein after IV scAAV9-SMN1 injection has to be assumed.

In an exploratory study in young NHP, IV injection of doses of 1-3×10^{14} vg/kg scAAV9.CB.GFP at PND1, PND30, or PND90 led to passage of scAAV9.CB.GFP through the BBB resulting in GFP transgene expression in glial cells throughout the brain, motor neurons within the spinal cord, and DRG. Systemic GFP expression was detected in all organs analysed, including skeletal muscle, the testes, heart, spleen, and small intestine. This distribution and expression pattern was further substantiated in an NHP pilot IV safety in 4 animals which were injected IV with 6.7×10^{13} vg/kg scAAV9-SMN1 at PND90. The animals were sacrificed at 9 months of age. Expression of SMN1 was noted in almost all tissues examined, with only the intestines showing little or no expression. In the 6-month toxicology study in NHP, the scAAV9-SMN1 viral vector distributed systemically and vector DNA and SMN1 mRNA persisted in tissues until 6 months post-dose, with the concentrations being higher at 6 weeks post-dose compared to 6 months post-dose.

No nonclinical shedding studies were performed. Instead, a detailed assessment of shedding in saliva, urine, and faeces was performed in humans.

5.3 Toxicology

The safety of a single IV infusion of scAAV9-SMN1 was assessed in non-GLP and GLP toxicology studies in female and male FVB mice and in cynomolgus monkeys. Two valid 3-month GLP toxicology study were performed in mice and 1 valid GLP 6-month toxicology study was performed in monkeys.

In the first mouse study, scAAV9-SMN1 viral vectors from a commercial batch were dosed on PND1 with 7.9×10^{13}, 2.37×10^{14}, and 3.91×10^{14} vg/kg. In control animals, 0.9% saline was infused. Mortality and adverse clinical signs were observed in mice administered the highest dose. Death was attributed to the formation of treatment-related thrombi in the heart in about half of the animals, while the cause of morbidity/death was considered to be undetermined in the other animals. A reduction in group mean body weight was observed in this same group over time, as compared with mice administered the control vehicle. Other findings included hunched posture, ungroomed fur, laboured or shallow breathing, cold to touch, thinness, and dark eyeball or closed eyes in some females. Minimal to mild changes in clinical pathology parameters were observed at all doses as early as Week 3, and were consistent with the induction of inflammation (increased lymphocytes, monocytes, eosinophils, and/or neutrophils, decreased reticulocytes). Increased transaminase activity and/or creatine kinase activities were possibly associated with microscopic findings of degeneration/regeneration in the heart and regeneration in the liver. The determined no adverse effect level (NOAEL) in this study was 2.37×10^{14} vg/kg.

In the second study, newborn mice were treated once on PND0 with either control vehicle or scAAV9-SMN1 viral vectors at dose levels of 1.5×10^{14} vg/kg, 2.4×10^{14} vg/kg, or 3.0×10^{14} vg/kg. scAAV9-SMN1-related mortalities were associated with atrial thrombus formation. Atrial thrombosis and associated atrial wall changes were dose-related and present in animals administered ≥2.4×10^{14}

vg/kg. Clinical pathology findings attributed to the moribund condition included slightly lower platelet count, glucose concentration, and cholesterol concentration and minimally to slightly higher alanine aminotransferase (ALT) activity and total bilirubin concentration. In the group receiving the highest dose, rough fur, irregular respiration, hypoactivity, hunched appearance, and protruding eyes were observed and considered adverse because they were consistent with the moribund conditions that led to the unscheduled deaths. Reductions in body weight were observed in all treatment groups. Adverse scAAV9-SMN1-related microscopic findings in the atria of the heart occurred and consisted of thrombus formation, dilation, fibroplasia, myocardial necrosis, and mononuclear cell inflammation. Reversible scAAV9-SMN1-related microscopic findings in the lungs of animals administered ≥2.4×10^{14} vg/kg consisted of minimal to slight perivascular inflammation and slight chronic inflammation. Test article-related microscopic findings in the liver consisted of minimal hepatocellular hypertrophy, minimally increased sinusoidal macrophages (Kupffer cells), minimal to slight individual hepatocyte necrosis, and minimal to slight perinuclear vacuolation of hepatocytes. A NOAEL was not determined in this study.

In the 6-month GLP toxicology study conducted in female and male juvenile NHP (14-15 months old), a single dose of scAAV9-SMN1 was administered at the clinically recommended intravenous dose of 1.1×10^{14} vg/kg, with or without prednisolone treatment. The scAAV9-SMN1 treatment was generally well tolerated for up to 6 months. Minor increases in plasma NfL concentrations and some clinical pathology findings were consistent with hepatocellular injury, decreased platelet count, and a mild inflammatory response and were fully or partially reversed by Day 176. The IV treatment with scAAV9-SMN1 resulted in the induction of antibodies against the viral vector. Adverse, test article-related microscopic findings of neuronal degeneration and mononuclear cell inflammation were present, but considered to be resolving and/or non-progressive in DRG and trigeminal ganglia (TG) following a 6-month observation period due to lower incidence and severity compared with the interim necropsy. The administration of oral prednisolone had no effect on the incidence, severity or distribution of microscopic findings related to scAAV9-SMN1. Based on the adverse microscopic DRG and TG observations, a NOAEL was not established.

Genotoxicity, carcinogenicity, and reproduction toxicity studies have not been conducted with onasemnogene abeparvovec, which can be accepted based on the disease indication, the applied viral vector type, and the therapeutic transgene. Although AAV viral vectors are non-integrative and remain primarily episomal, very rare viral vector integration events in the genome of transduced cells cannot be completely excluded.

5.4 Nonclinical conclusions

In the SMNΔ7 SMA mouse model, a single IV treatment with scAAV9-SMN1 resulted in long-term survivial[1]. Biodistribution studies showed that the scAAV9 viral vector crossed the BBB, but a substantial transduction of motor neurons was only observed in newborn mice. In adult animals, scAAV9 transduced mainly glial cells in the brain.

The scAAV9-SMN1 viral vector showed systemic biodistribution after IV injection in all organs analysed. Besides scAAV9 vector distribution and SMN1 transgene expression in the central nervous system, the highest vector and SMN1 expression levels were found in the heart, liver, lung, and skeletal muscle. This systemic distribution may result in clinically beneficial expression of SMN1 protein in peripheral organs in SMA patients. Unphysiological overexpression of SMN1 protein after scAAV9-SMN1 transduction may pose a potential risk, resulting in cell and tissue damage and the induction of an inflammatory response. The risk of scAAV9 vector biodistribution and SMN1 protein expression in gonads was not assessed in detail nonclinically. However, lack of more detailed germline transmission studies can be accepted based on the absence of critical findings in gonads in the context of the nonclinical toxicological evaluations and based on the severity of the disease indication and the target population.

In mice, the main target organs of toxicity identified were the liver and the heart. Liver findings in mice consisted of hepatocellular hypertrophy, Kupffer cell activation, scattered hepatocellular necrosis, and elevated blood transaminase levels. The scAAV9-SMN1-related findings in the ventricles of the heart consisted of dose-related inflammations, oedema, and fibrosis. In the atria of the heart, inflammation, thrombosis, myocardial degenerations, necrosis, and fibroplasia were observed. High doses of scAAV9-SMN1 caused mortality in FVB mice due to atrial thrombosis. A NOAEL was not identified as ventricular heart effects were also observed at the lowest dose tested (1.5×10^{14} vg/kg). This dose is regarded as the maximum tolerated dose (MTD) and it has only a small safety margin of 1.4-fold with respect to the recommended human clinical dose. In view of such a narrow therapeutic window, it is critical that batch-to-batch variations in the final product need to be carefully monitored and assessed.

In the 2 relevant 12-week mouse toxicology studies, no antibodies against the scAAV9-SMN1 viral vector or against the SMN1 protein were analysed. However, in a 24-week mouse toxicology study that was performed with research-grade scAAV9-SMN1, the IV treatment induced an immune response against the viral vector. Therefore, it can be assumed that IV treatment with the scAAV9-SMN1 viral vector induces an immune response, which may explain some of the observed inflammatory responses.

In the 6-month toxicology study in NHP, the IV scAAV9-SMN1 was well tolerated. Reversible effects were observed such as liver injury, decreased platelet count, and mild inflammatory responses. As in mice, the viral vector treatment induced antibodies against the viral vector. Partially reversible neuronal degeneration and mononuclear cell inflammation were identified in DRG and TG.

In conclusion, the nonclinical evaluation of Zolgensma showed clear efficacy, a systemic biodistribution, and a defined toxicology profile after IV infusion. In human clinical studies the heart effects were not identified and the liver effects were considered manageable. Possible consequences with respect to inflammatory effects in DRG and TG need to be monitored clinically. SMA is a very severe childhood disease with a lethal outcome in its most severe forms. Therefore, Zolgensma can be approved from the nonclinical point of vie

[1] *At the time of the initial Marketing Authoriszation Application (MAA), the Zolgensma dossier included discussions and references to an early research in vivo SMNΔ7 mouse disease research model study published in Nature Biotechnology in 2010 (Foust et al., 2010 'Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN', Nature Biotechnology (vol. 28 no. 3 Mar 2010 ppg. 271-4). Data integrity findings were later discovered and notified by Novartis to the Health Authorities. Given that Novartis was not the sponsor of this study, when it became aware of the situation in 2021, the company communicated to the first author and academic institution that the publication should be corrected or retracted. Nature Biotechnology took an independent decision and have decided to retract this publication (06-Oct-2022);, a decision Novartis supports. A regulatory impact assessment was conducted by Novartis for the data discussed in the original MAA. The assessment confirmed there is no impact on the clinical safety and efficacy results, the benefit- risk conclusions in the dossier, or the approved/proposed product information.*

6 Clinical aspects

6.1 Clinical pharmacology

6.1.1 Pharmacokinetics

ADME

Conventional clinical PK studies are not possible for a viral gene therapy product. In humans, the presence of the viral vector in blood, shedding, and immunogenicity are investigated.

Biodistribution
Zolgensma is administered intravenously.
The adeno-associated virus serotype 9 (AAV9) viral vector carries the SMN gene and is designed for non-integration into the host genome. The SMN gene resides as a deoxyribonucleic acid (DNA) episome in the nucleus of transduced cells.
Biodistribution was evaluated in pre-clinical studies and in 2 cases where an autopsy was performed on a deceased patient. 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 muscle, peripheral nerves, kidney, lung, intestines, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalised SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscle, and other tissues evaluated.

Viral shedding and excretion
Onasemnogene abeparvovec vector shedding studies, which assessed the amount of vector eliminated from the body through saliva, urine, and faeces, confirmed that onasemnogene abeparvovec is detectable in shedding samples post-infusion. Clearance of onasemnogene abeparvovec is primarily via faeces and the majority is cleared within 30 days after dose administration. Onasemnogene abeparvovec concentrations in urine and saliva were 0.1% to 0.01% of the initial concentration in the body at Day 1 post-infusion and dropped thereafter. The risk of adverse effects in healthy humans after shedding is considered low. See warnings and precautions in the Information for healthcare professionals (Appendix 8 of this document).

Immunogenicity
As expected, an immunological response was observed against AAV9 after intravenous administration of Zolgensma. The immunological response is expected to be transient, but based on the long-term data derived from CL-101 and LT-001 seems to be sustained. No immunological response was observed against hSMN.

Interactions
No interaction studies have been carried out.
Because of liver toxicity caused by Zolgensma, patients receiving hepatotoxic medication may be at increased risk, and safety in these patients has not been established. For concomitant vaccinations, see the Information for healthcare professionals.

6.1.2 Pharmacodynamics

Mechanism of action and primary pharmacology
Onasemnogene abeparvovec is a gene therapy designed to introduce a functional human copy of the survival motor neuron (SMN1) gene into the transduced cells. The SMN1 gene is delivered by a **non-replicating**, **non-pathogenic** recombinant AAV9 (adeno-associated virus serotype 9) vector, whose capsid (the protein shell of the virus that encloses its genetic material) contains the transgene: it is a genetically modified organism (GMO).

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. 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 in the motor neurons. The LTFU studies will have to confirm that efficacy does indeed last long-term.

6.2 Dose finding and dose recommendation

The approved dose is 1.1 × 10^{14} vg/kg onasemnogene abeparvovec. No specific dose response study was conducted. The recommended dose is based on nonclinical data and on the Phase 1 type 1 SMA clinical study CL-101.
Study CL-101 (AVXS-101-CL-101) was a monocentric study (USA) and included 15 clinically symptomatic patients aged 6 months or less with bi-allelic SMN1 mutations and 2 copies of the SMN2 gene without c.859G>C modification (a positive disease modifier). The study was open label and the participants received a single IV infusion. Two cohorts were treated and the study was completed in December 2017:

- Cohort 1: 3 patients received 6.7 E13 vg/kg
- Cohort 2: 12 patients received 2.0 E14 vg/kg

The patients (6 males and 9 females) were followed for 2 years. At the time of study drug administration, they were aged between 0.9 and 7.9 months (median 4.1 months). They had been diagnosed with type 1 SMA between birth and 6 months of age.
The primary objective was safety. The primary efficacy endpoint was survival, defined as time from birth to death or permanent ventilation (defined as ventilatory support for greater than 16 hours a day). The primary efficacy data cutoff was the date at which all patients had completed a study visit after reaching 13.6 months of age (20 January 2017). As of the primary efficacy data cutoff, all 15 patients (100%) were surviving event-free, while the natural history cohort rate would be 25%.
For Cohort 2, on the CHOP-INTEND scale, 11/12 patients achieved scores > 40. 11/12 patients could hold their head erect for > 3 seconds, 5/12 patients sat for > 30 seconds without assistance, 2/12 patients (16.7%) could walk alone. The CHOP-INTEND (the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders) score is a sensitive score for motor function ability designed and validated specifically for severely affected SMA patients. The patients are scored on 16 items (including joint flexion and extension, spontaneous movement, and head control), ranging from 1-4 per item. This gives a total maximum score of 64. The CHOP-INTEND score represents measures of disease severity.

Three dose levels were pre-planned (6.7E13 vg/kg, 2.0E14 vg/kg, and 3.3E14 vg/kg). The highest was never used as the second dose level exceeded expectations with motor milestone achievement never seen in the natural course of the disease. This is also the dose selected for the pivotal study CL-303.

Study LT-001 is an ongoing 15-year observational follow-up of study CL-101, with 13 of the original patients included. Medical history, physical examination, and clinical laboratory data are being followed up.

6.3 Efficacy

Study CL-303 (AVXS-101-CL-303) is a Phase 3 **pivotal** study of intravenous administration of onasemnogene abeparvovec at the therapeutic dose of 1.1 × 10^{14} vg/kg. Because manufacturing process A was changed to manufacturing process B early in clinical development, a single IV infusion of 1.1E14 vg/kg was considered to be "equivalent" to the dose of 2.0 E14 vg/kg used in Cohort 2 of study CL-101.

Twenty-two patients with type 1 SMA and 2 copies of SMN2 were enrolled. Patient ages at administration ranged from 0.5 to 5.9 months. The study was an open-label, single-arm, single-dose study. The patients had to be either symptomatic or pre-symptomatic with no functional SMN1 gene

and no more than 1 or 2 copies of SMN2, and had to be < 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1).
Of the 22 patients treated, 10 were males and 12 females, with a median age of 3.5 months (min. 0.5 months, max. 5.9 months) at the time of the study drug infusion.
There were 2 co-primary endpoints:

- survival at 14 months of age
- the proportion of patients who achieved functional independent sitting for ≥ 30 seconds at the 18 months of age study visit.

Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement for ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation defined in this way is considered as a surrogate for death.
Without treatment, SMA type 1 patients can expect a life expectancy of less than 2 years.
The ITT population consisted of symptomatic patients with bi-allelic deletion mutations of SMN1 (exon 7/8 common homozygous deletions) and 2 copies of SMN2 without the known gene modifier mutation (c.859G>C) who received an IV infusion of AVXS-101 at < 180 days of age. All patients met the ITT criteria

Of the 22 enrolled patients, 20 patients (90.9%) had survived event-free (no permanent ventilation and no death) at 18 months of age.
Out of those 20 patients, 2 patients had head control at baseline. After receiving AVXS-101, an additional 17 patients achieved head control, 13 patients (59.1%) achieved rolls from back to side, and 14 patients (63.6%) achieved sitting without support for at least 30 seconds (Bayley Scales definition). In addition, 1 patient achieved the motor milestones of crawls, pulls to stand, stands with assistance, walks with assistance, stands alone, and walks alone as defined by the Bayley gross motor scale.
This compares favourably to historical controls, who as a rule require permanent ventilation and/or die before reaching the age of 2, and, in a large proportion of cases, before reaching 1 year of age.
It should be noted, however, that all patients in this study were treated before reaching 6 months of age. As a rule, in patients with SMA, the earlier the disease is treated, the larger the observed treatment effect. It is therefore difficult to extrapolate the CL-303 results to subjects with SMA type 1 treated after reaching the age of 6 months.

Study CL-304 is an ongoing multi-centre, global, Phase III, open label, single arm study to assess the safety and efficacy of a single IV infusion of 1.1E14 vg/kg (equivalent to therapeutic dose Cohort 2 CL-101). The target patient population is pre-symptomatic patients expected to develop SMA, bi-allelic deletion of SMN1 and 2, 3, or 4 copies of SMN2 without the genetic modifier (c.895G>C) (ITT population).

6.4 Safety

Undesirable effects include hepatotoxicity ranging from aminotransferase elevations (very common) to potentially fatal acute liver failure (post-marketing). Also commonly observed are thrombocytopenia, elevated troponin-I, vomiting, and pyrexia. Post-marketing, thrombotic microangiopathy including fatal cases has been reported.
Initiation of an immunoregulatory regimen prior to administration of Zolgensma is recommended, as is baseline laboratory testing and close monitoring of liver function, platelet count, and troponin-I after administration. Also, it is unclear how the presence of anti-AAV9 titres > 1:50 at baseline would affect treatment with Zolgensma, since such patients were excluded from the studies. See current Information for healthcare professionals.

Since Zolgensma has been given conditional authorisation, the company that markets Zolgensma will provide additional data on its benefits and risks. These include data from 2 studies in patients younger

than 6 months with SMA type I and 1 study in patients younger than 6 weeks who do not have symptoms but for whom the diagnosis of SMA is confirmed based on genetic testing.

6.5 Final clinical benefit-risk assessment

Conclusions: clinical assessment
The benefit-risk assessment is positive, at least for very young patients with SMA type 1 treated before the age of 6 months and for pre-symptomatic patients with 2 (or 3) copies of SMN2 treated before the age of 6 weeks. The improvements in survival, need for ventilation, and motor milestones clearly override the risks, which can as a rule be controlled by the administration of corticosteroids and frequent monitoring. Also, the corticosteroids can usually be stopped within the 3 months following Zolgensma administration. Zolgensma is given only once. This is in contrast to an approved splicing modifier of SMN2 pre-mRNA, which has to be given orally once daily, and in contrast to an approved antisense oligonucleotide (ASO), which has to be given intrathecally every 4 months. Overall, the ratio of benefits to risks in the treatment of patients up to the age of 2 years 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 is considered favourable.

Conclusions: clinical pharmacology
There were no major pharmacokinetic/pharmacodynamic issues associated with onasemnogene abeparvovec.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Zolgensma was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Zolgensma has been approved on a temporary basis; see “Properties/Actions”.

Zolgensma®

Composition

Active substances

Onasemnogene abeparvovec: 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.

Consists of a genetically modified adeno-associated viral vector serotype 9 (scAAV9).

Excipients

Tromethamine, magnesium chloride, 11.7 mg sodium chloride/ml (equivalent to 4.6 mg sodium/ml), poloxamer 188, hydrochloric acid (for pH adjustment), water for injections

Pharmaceutical form and quantity of active substance per unit

Solution for infusion for intravenous (IV) administration.
When thawed, it is a clear to slightly opaque, colourless to faint white solution.

Each ml contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg). The vials contain an extractable volume of not less than 5.5 ml or 8.3 ml. The total number of vials and combination of fill volumes in a finished pack are customised to the dosing requirements of individual patients depending on their body weight (see “Dosage/Administration” and “Pack sizes”).

Indications/Potential uses

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.

Therapy may only be administered up to the age of two years.

Dosage/Administration

Zolgensma may only be administered in hospital-based, specialised neuromuscular centres. Treating healthcare professionals must have experience in the diagnostics and treatment of patients with spinal muscular atrophy.
Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including:

- AAV9 antibody testing using an appropriately validated assay
- Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin
- 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 levels after administration and the required concomitant corticosteroid treatment must be taken into account when establishing the timing of onasemnogene abeparvovec therapy (see “Warnings and precautions”).

If acute or chronic, uncontrolled active infections are present, treatment should be postponed until the infection has resolved or is controlled. Clinical signs or symptoms of infection must not be present at the time of onasemnogene abeparvovec administration (see “Dosage/Administration” and “Warnings and precautions”, “Immunomodulatory regimen”).
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product must be clearly documented.

Usual dosage

For single-dose intravenous infusion only.

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

Table 1 gives the recommended dosing for patients with a body weight of 2.6 kg to 16.0 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
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

[a] Note: Number of vials per kit and required number of kits are weight-dependent. Dose volume is calculated using the upper limit of the patient weight range in paediatric patients up to the age of two years.

Immunomodulatory regimen

An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after administration of onasemnogene abeparvovec (see “Warnings and precautions”). This can lead to elevations in liver aminotransferases, elevations in troponin I levels or decreased platelet counts (see “Warnings and precautions” and “Adverse effects”). 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 "Interactions").

Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec the patient must be checked for 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). Deviations from these recommendations are at the discretion of the treating physician (see "Warnings and precautions").

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 findings, total bilirubin, and whose ALT and AST values are both below 2 × upper limit of normal (ULN)) at the end of the 30-day period:* **or** *For patients with liver function abnormalities at the end of the 30-day period: continuing until AST and ALT values are below 2 × ULN and all other assessments return to normal range, followed by tapering over 28 days or longer if needed.*	Systemic corticosteroids should be tapered gradually. Tapering of prednisolone dose (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 should be monitored for at least 3 months following onasemnogene abeparvovec infusion (see "Warnings and precautions")	

A paediatric gastroenterologist or hepatologist should be consulted if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone (see "Warnings and precautions"). If oral corticosteroid therapy is not tolerated, an intravenous corticosteroid may be considered as clinically indicated.

If the treating physician uses another corticosteroid in place of prednisolone, similar considerations and approaches to taper the dose after 30 days should be applied as appropriate.

Special populations

Patients with hepatic impairment

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

Patients with 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.

Children and adolescents

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.

In clinical studies patients up to 6 months of age (and up to a weight of 8.5 kg) were treated . There are no controlled data from patients aged between 6 months and 2 years at the time of treatment. The safety and efficacy of onasemnogene abeparvovec outside of the study population can therefore only be partially established based on current data and only up to an age of two years. Currently available data are described under “Properties/Actions”.

0SMN1/1SMN2 genotype

No clinical data are available for patients with a bi-allelic mutation of the *SMN1* gene and only one copy of *SMN2* (see “Properties/Actions”).

AAV9 antibodies

No dose adjustment should be considered in patients with baseline AAV9 antibody titres above 1:50 (see “Warnings and precautions”). In the clinical studies no patients with AAV9 antibody titres above 1:50 were treated.

Method of administration

For intravenous use.
Onasemnogene abeparvovec should be administered with a syringe pump as a single slow intravenous infusion over a period of approximately 60 minutes and must not be administered as a rapid intravenous infusion 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 saline solution.
For instructions on dilution of the medicinal product before administration, see “Other information”.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains a genetically modified organism. Personal protective equipment (i.e. gloves, safety goggles, laboratory coat and sleeve protectors) should be worn when preparing and administering onasemnogene abeparvovec (see “Other information”).

For instructions on preparation, handling, accidental exposure and disposal of the medicinal product see “Other information”.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

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 of onasemnogene abeparvovec. Re-testing may be performed if AAV9 antibody titres are above 1:50. It is not yet known whether or under what conditions onasemnogene abeparvovec can be safely and effectively administered when anti-AAV9 antibody titres are above 1:50 (see “Dosage/Administration” and “Properties/Actions”).

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 a potentially greater benefit.
Zolgensma has not been studied in patients with severe hypotonia and respiratory failure at birth or at the time of treatment. It is unlikely that such patients would derive a clinically meaningful benefit from treatment with Zolgensma.
The treating physician should take this into consideration. Furthermore, patients with profound muscle weakness and respiratory failure, patients on permanent ventilation and patients not able to swallow were not included in the clinical studies.
The benefit-risk profile of onasemnogene abeparvovec in patients with advanced SMA kept alive through permanent ventilation and without the ability to thrive is unknown.

No data are available on the long-term efficacy of this medicinal product.

Immunogenicity

An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid occurs after infusion of onasemnogene abeparvovec. This includes antibody formation against the AAV9 capsid, despite the immunomodulatory regimen recommended under “Dosage/Administration”, and a T-cell mediated immune response.

A systemic immune response, including immune-mediated hepatotoxicity, generally manifested as elevated ALT and/or AST levels and at times as acute serious liver injury or acute liver failure, has been reported with onasemnogene abeparvovec use. Immune-mediated hepatotoxicity may require adjustment of the immunomodulatory regimen in the form of a longer duration, increased dose or prolongation of the corticosteroid taper. For details on the immunomodulatory regimen see the "Dosage/Administration" section and the "Hepatotoxicity" and "Immunomodulatory regimen" subsections below.

Hepatotoxicity

- Administration of an AAV vector may result in aminotransferase elevations, which may be serious.
- Acute serious liver injury and acute liver failure have occurred (see "Adverse effects").
- Patients with pre-existing hepatic impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury (see "Dosage/Administration").
- Prior to infusion patient liver function should always be assessed by clinical examination and laboratory testing (e.g. hepatic aminotransferases AST and ALT and total bilirubin (see "Dosage/Administration")).
- In order to mitigate potential aminotransferase elevations, each patient should be treated with a systemic corticosteroid before and after onasemnogene abeparvovec infusion (see "Dosage/Administration").
- Liver function should be monitored for at least 3 months after infusion.
- The risks and benefits of onasemnogene abeparvovec infusion in patients with pre-existing hepatic impairment should be weighed carefully against the risks of not treating the patient.

AST/ALT/total bilirubin should be assessed weekly for 30 days and every two weeks for an additional 60 days post administration of onasemnogene abeparvovec until the end of the corticosteroid taper period, or longer if needed. Tapering of prednisolone should not be considered until AST/ALT levels are less than 2 × ULN.

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 in the first week following onasemnogene abeparvovec infusion. Platelet counts should be obtained before onasemnogene abeparvovec infusion and monitored regularly thereafter – weekly in the first month and every other week in the second and third months – until platelet counts return to baseline.

Thrombotic microangiopathy

Post-marketing cases of thrombotic microangiopathy (TMA) have been reported approximately one week after onasemnogene abeparvovec infusion (see “Adverse effects”). TMA is characterised by thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury. In some cases concurrent immune system activation (e.g. via infections, vaccinations) was identified as a contributing factor.
Thrombocytopenia is a key feature of TMA; therefore, platelet counts should be monitored (see “Thrombocytopenia” subsection) and patients should be monitored for 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 evaluations for haemolytic anaemia and renal impairment should be undertaken. In the event of clinical signs, symptoms and/or laboratory findings consistent with TMA, a specialist should be consulted immediately to manage TMA as clinically indicated.

Elevated troponin I

Increases in cardiac troponin I levels following infusion of onasemnogene abeparvovec have been observed (see “Adverse effects”). 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 in SMA patients should be obtained before onasemnogene abeparvovec infusion and monitored for at least 3 months thereafter or until levels return to within the normal reference range. Consultation of a cardiologist should be considered as needed.

Immunomodulatory regimen

Immunomodulatory treatment should not be initiated concurrently with active infections. This applies both to acute infections (such as acute respiratory infections or acute hepatitis) and uncontrolled chronic infections (such as chronic active hepatitis B) (see “Dosage/Administration” and “Warnings and precautions”).

The immunomodulatory regimen (see “Dosage/Administration”) might also impact the immune response to concurrent infections (e.g. respiratory), potentially resulting in more severe clinical courses of existing infections. Added caution is required regarding the timing of onasemnogene abeparvovec dosing in the presence of prodrome or resolving infection. Increased vigilance in the diagnosis and active management of infection is recommended. 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 “Interactions”).

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.

Shedding

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

- Good hand hygiene is required when coming into direct contact with patient bodily fluids and stools. These instructions must be followed 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.

Sodium content

This medicinal product contains 75.9 to 531.3 mg sodium per dosage unit, equivalent to 3 to 26% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

No interaction studies have been performed.

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

Experience with use of concomitant 5q SMA-targeting agents is limited. There are no interpretable data on the efficacy or safety of combination treatment.

Other interactions

Vaccinations

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

Pregnancy/Breast-feeding

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

Effects on ability to drive and use machines

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

Adverse 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 effects following administration were increased hepatic enzymes (24.2%), hepatotoxicity (9.1%), vomiting (8.1%) and pyrexia (5.1%) (see “Warnings and precautions”)

Tabulated list of adverse effects

The adverse effects that occurred with onasemnogene abeparvovec in all patients who received an intravenous infusion at the recommended dose with a causal association with treatment are presented in Table 3. Adverse effects are presented according to MedDRA system organ classification and ordered by frequency. Frequency categories are based on the following convention: 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 (frequency cannot be estimated from the available data). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Table 3: List of adverse effects of onasemnogene abeparvovec

Adverse effects by MedDRA SOC/PT and frequency	
Blood and lymphatic system disorders	
Common	Thrombocytopenia
Not known	Thrombotic microangiopathy[1)]
Gastrointestinal disorders	
Common	Vomiting
Hepatobiliary disorders	
Common	Hepatotoxicity[2)]
Not known	Acute liver failure[1)]
Not known	Acute liver injury[1)]
General disorders and administration site conditions	
Common	Pyrexia
Investigations	
Very common	Increased hepatic enzymes[3)] (24.2%)
Common	Increased troponin[4)]
Common	Increased troponin T
Common	Decreased platelet count

[1)]Treatment-related adverse effects reported outside of clinical studies and in the post-marketing setting.
[2)]Hepatotoxicity includes hepatic steatosis and hypertransaminasaemia.
[3)]Increased hepatic enzymes includes: increased alanine aminotransferase, increased ammonia, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased hepatic enzymes, increased liver function test and increased transaminases.
[4)]Increased troponin includes increased troponin I and increased troponin T.

Description of selected adverse effects

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 showed clinically significant elevations of bilirubin. Serum transaminase elevations usually resolved with prednisolone treatment and patients recovered without clinical sequelae (see “Dosage/Administration” and “Warnings and precautions”). In the post-marketing setting, outside of clinical studies, there have been reports of children developing signs and symptoms of acute liver failure (e.g. jaundice, coagulopathy, encephalopathy) within the first two months of treatment with onasemnogene abeparvovec, despite receiving corticosteroids before and after infusion. According to the case reports a modified treatment regimen with corticosteroids was given after liver failure was diagnosed. These children recovered.

Transient thrombocytopenia
In clinical studies transient decreases from baseline in mean platelet counts (4.0%) 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 following treatment (see “Warnings and precautions”).

Increases in troponin I levels
Increases in cardiac troponin I levels (3.0%) up to 0.2 µg/l following onasemnogene abeparvovec infusion have been observed. In the clinical study program no clinically apparent cardiac findings were observed following administration of onasemnogene abeparvovec (see “Warnings and precautions”).

Immunogenicity
Pre- and post-gene therapy titres of anti-AAV9 antibodies were measured in the clinical studies (see “Warnings and precautions”). 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 one time point in relation to the AAV9 peptide, which is the normal response to a non-self viral antigen. Some patients exhibited AAV9 titres exceeding the level of quantification; however, most of these patients did not have potentially clinically significant adverse effects. Thus, no relationship has been established between high anti-AAV9 antibody titres and the potential for adverse effects or efficacy parameters.
In the AVXS-101-CL-101 clinical study 16 patients were screened for anti-AAV9 antibody titres: 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 then measured at less than 1:50 and both were enrolled in the study. There is no information on whether breast-feeding should be restricted in mothers who may be seropositive for anti-AAV9 antibodies. Patients all had AAV9 antibody titres less than or equal to 1:50 prior to treatment with onasemnogene abeparvovec and subsequently demonstrated an increase in 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 such as assay methodology, sample handling, timing of sample collection, co-medication and underlying disease.
No onasemnogene abeparvovec-treated patient demonstrated an immune response to the transgene.
Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

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

Properties/Actions

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*) into the transduced cells to treat 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 AAV9 vector that utilises an 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 into target cells as a self-complementary, double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (hybrid of cytomegalovirus enhancer and chicken β-actin promoter), which results in continuous and sustained SMN protein expression. Proof of the mechanism of action is supported by preclinical studies and by human biodistribution data.

Pharmacodynamics

Not applicable.

Clinical efficacy

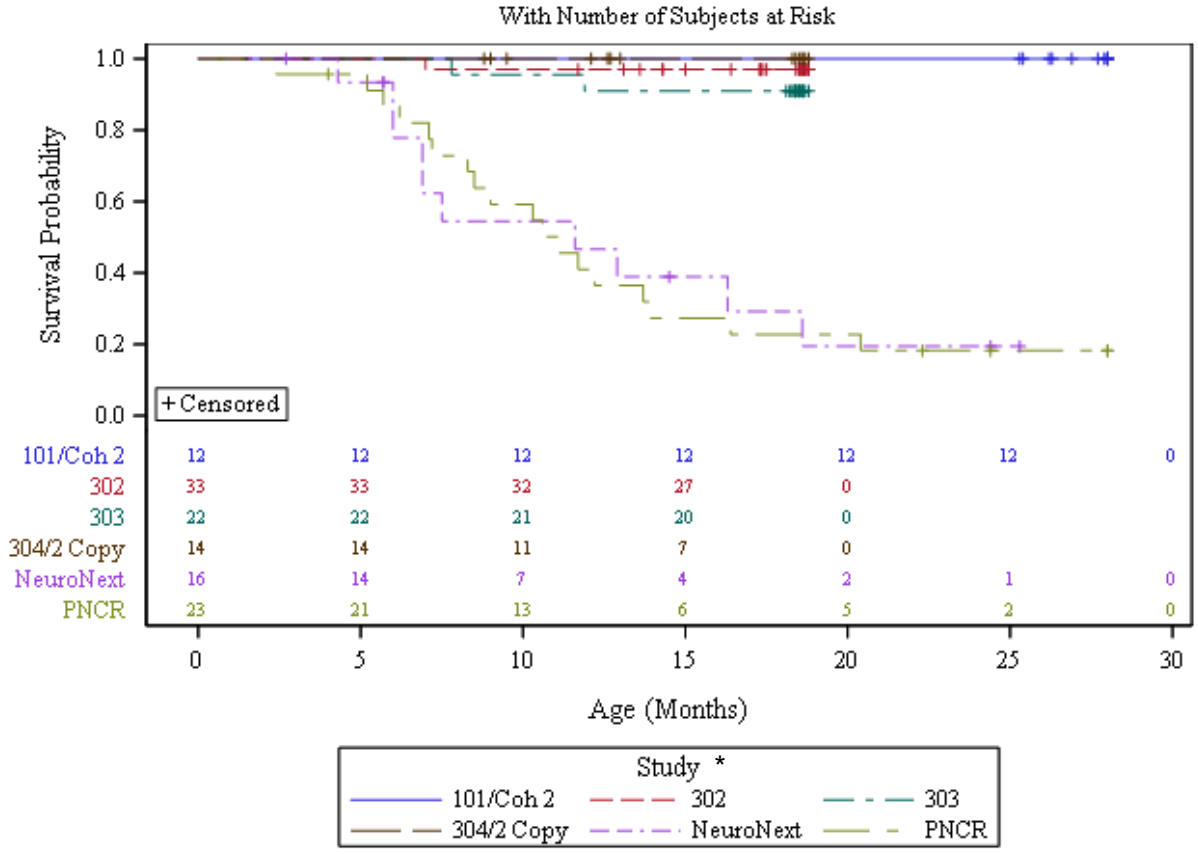
AVXS-101-CL-303 phase 3 study in patients with SMA type 1
AVXS-101-CL-303 (study CL-303) is a phase 3, open-label, single-arm, single-dose study of intravenous administration of onasemnogene abeparvovec at the therapeutic dose (1.1×10^{14} vg/kg). 22 patients were enrolled with SMA type 1 and 2 copies 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 (range 0.5 to 5.9 months).

Of the 22 enrolled patients, 21 patients survived without permanent ventilation (event-free survival) to ≥10.5 months of age, 20 patients survived to ≥14 months of age event-free (co-primary efficacy endpoint) and 20 patients to 18 months of age.

Three patients did not complete the study. Two of them 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).

Figure1: Time (in 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
* AVXS-101-CL-302 is an ongoing phase 3, multicentre, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) in patients with SMA type 1 with 1 or 2 copies of the *SMN2* gene, similar to study AVXS-101-CL-303. At the time of the 11 June 2020 data cut-off the 33 enrolled and treated patients had been in the study for an average of 13.07 months (between 1.8 and 16.4 months).

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).

The milestone of independent sitting for at least 30 seconds was confirmed in 13 patients (59.1%) 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 18-month 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 three patients (13.6%) achieved head control as the maximum motor milestone before the final study visit at 18 months of age.

Table 4: Median time to video-documented achievement of motor milestones, study CL-303

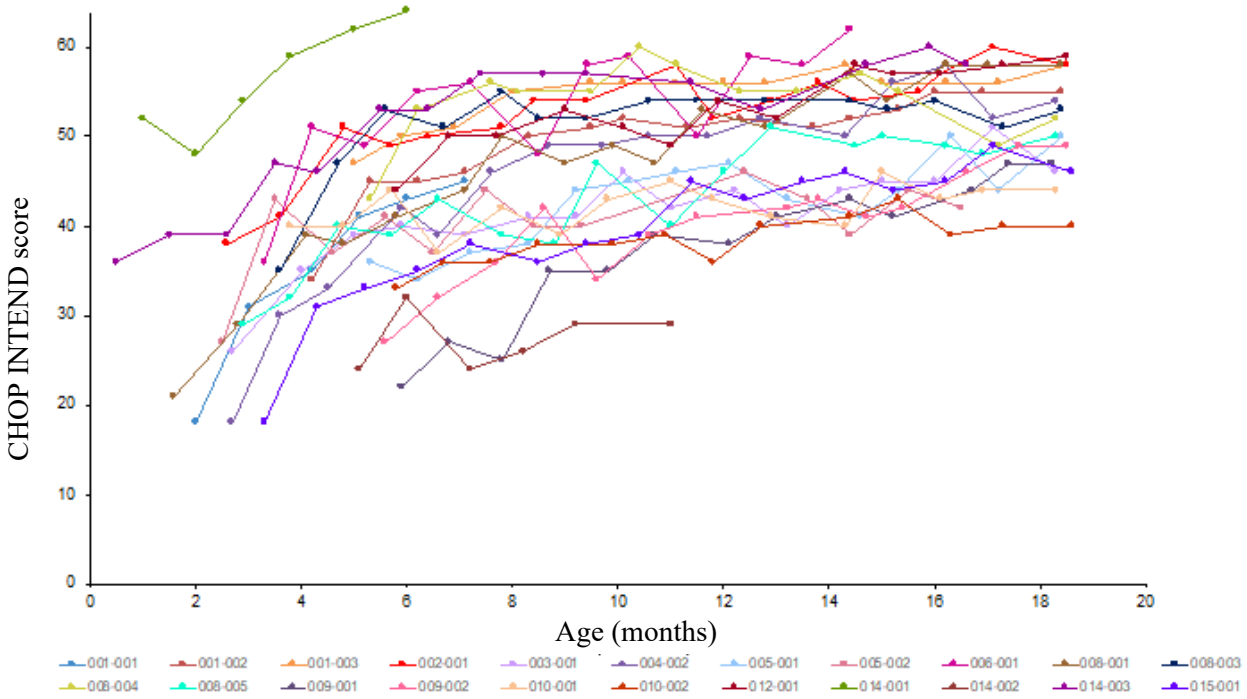
Video-documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (months)	95% confidence interval
Head control	17/20* (85.0)	6.8	(4.77, 7.57)
Rolls from back to sides	13/22 (59.1)	11.5	(7.77, 14.53)
Sits without support for 30 seconds (Bayley)	14/22 (63.6)	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 were not 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.

Improvement in motor development was also observed, as measured by the CHOP-INTEND (see Figure 2). 21 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 milestones were achieved 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 development scores, study CL-303



AVXS-101-CL-101 phase 1 study in patients with SMA type 1

The results from study CL-303 are supported by study AVXS-101-CL-101 (study CL-101), a phase 1 study in patients with SMA type 1 in which onasemnogene abeparvovec was administered as a single intravenous infusion in 12 patients with a body weight 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 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. 1 of 12 patients did not achieve head control as the maximum motor milestone before the age of 24 months. 10 of 12 patients from study CL-101 continue to be followed in a long-term study (for up to 5.5 years after dosing). All have either maintained previously attained milestones or achieved new milestones, including sitting with support, standing with assistance and walking alone. 4 of the 10 patients received concomitant nusinersen 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 achieved by two patients who were not receiving nusinersen.

AVXS-101-CL-304 phase 3 study in patients with pre-symptomatic SMA

Study CL-304 is an ongoing, global, phase 3, open-label, single-arm, single-dose, multicentre study of IV AVXS-101 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
At the time of the last study visit prior to 11 June 2020 the 14 treated patients with 2 copies of *SMN2* had a median age of 15.6 months (range: 8.8 to 18.8 months) and had been in the study for a median of 14.9 months (range: 8.0 to 18.4 months). All patients were alive and did not require permanent ventilation as of their last study visit prior to 11 June 2020.
11 patients achieved independent sitting for at least 30 seconds at ages from 5.7 to 11.8 months, with 10 of the 11 patients achieving independent sitting at or before 9.2 months of age, the 99th percentile for development of this milestone. 4 patients achieved the milestone of walking alone (28.6%).
13 patients (92.9%) achieved a CHOP-INTEND score ≥58 as of the 11 June 2020 data cut-off.

Cohort 2
At the time of the last study visit prior to 11 June 2020 the 15 treated patients with 3 copies of *SMN2* had a median age of 15.2 months (range: 3.3 to 21.1 months) and had been in the study for a median of 14.5 months (range: 2.0 to 19.9 months). All patients were alive and did not require permanent ventilation as of their last study visit prior to 11 June 2020.
13 of 15 patients were able to sit without support for at least 30 seconds, 8 patients were able to stand alone without support for at least 3 seconds and 6 patients were able to walk at least five steps without assistance.
At the time of the 11 June 2020 data cut-off patients with 3 copies of *SMN2* who had not yet achieved the cohort 2 primary endpoint developmental milestone of standing alone without support for at least 3 seconds were 3.3 to 16.4 months of age as of the last attended visit. Based on the age at the time of the last attended visit, these patients remain within the normal age development window for these milestones.
Due to the large heterogeneity in the clinical presentation of patients with 3 *SMN2* copies no definitive conclusions about the benefit in this patient population can be drawn.

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.

Temporary marketing authorisation

As the clinical data were incomplete at the time of the review of the marketing authorisation application, Zolgensma® has been approved on a temporary basis (Art. 9a of the Therapeutic Products Act). The temporary marketing authorisation is mandatorily associated with the prompt fulfilment of relevant conditions. Upon their fulfilment the temporary authorisation can be converted to a standard marketing authorisation.

Pharmacokinetics

Onasemnogene abeparvovec is a viral gene therapy product for intravenous use. Conventional clinical pharmacokinetic studies are therefore not applicable. No *in vitro* pharmacokinetic studies were performed in human cells, tissues or similar materials (human biomaterials).

Absorption

Not applicable.

Distribution

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec at a 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 generalised SMN expression in spinal motor neurons, neurons and glial cells of the brain, and in the heart, liver, skeletal muscles and other tissues evaluated.

Metabolism

Not applicable.

Elimination

Onasemnogene abeparvovec vector shedding studies assessing 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, with the majority cleared within 30 days after administration.

Preclinical data

Following intravenous administration in neonatal mice, vector and transgene were widely distributed, with the highest expression generally observed in the heart and liver and substantial expression observed in the brain and spinal cord. 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 comprised dose-related inflammation, oedema and fibrosis. In the atria of the heart, inflammation, thrombosis, myocardial degeneration/necrosis and fibroplasia were observed. Liver findings comprised hepatocellular hypertrophy, Kupffer cell activation and scattered hepatocellular necrosis. 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 corresponds to 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 a dose of 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.

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

In a toxicology study conducted in young adult non-human primates intrathecal administration of a single onasemnogene abeparvovec dose of 3×10^{13} vg/NHP (median dose 1.08×10^{13} vg/kg) in the Trendelenburg position, without corticosteroid treatment, resulted in minimal to marked mononuclear cell inflammation (primarily lymphocytes) in some dorsal root ganglia from all examined spinal cord levels, with neuronal satellitosis, neuronal necrosis or complete neuronal loss with rare mineralisation. The clinical relevance of this finding is unknown.

Other information

Incompatibilities

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

Shelf life

1 year at ≤-60°C
Do not use after the expiry date (= EXP) printed on the container.

Shelf life after thawing

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

Shelf life after opening

Once the dose volume is drawn into the syringe, it must be administered within 8 hours. If the medicinal product is not infused within 8 hours, the vector-containing syringe must be discarded.

Special precautions for storage

Store and transport frozen (≤-60°C).
Store in a refrigerator (2°C to 8°C) immediately upon receipt.
For storage conditions after thawing of the medicinal product, see “Shelf life after thawing”.

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

Instructions for use and handling

This medicinal product contains genetically modified organisms. Appropriate precautions for the handling and disposal of onasemnogene abeparvovec and for cases of accidental exposure must be followed:

- The onasemnogene abeparvovec syringe must be handled aseptically and prepared under sterile conditions.
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeve protectors) should be worn when handling and administering onasemnogene abeparvovec. Persons with skin injuries or scratches must not work with onasemnogene abeparvovec.
- Spills of onasemnogene abeparvovec must be wiped up with absorbent gauze pad. The affected area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of as per 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 contact with the eyes the affected area must be thoroughly flushed with water for at least 15 minutes.

Receipt and thawing of onasemnogene abeparvovec vials

- The vials will be transported frozen (≤-60ºC). Upon receipt the vials should be immediately stored in a refrigerator at 2°C to 8°C and kept in the original pack. Onasemnogene abeparvovec therapy must be initiated within 14 days of receipt of the vials.
- The vials must be thawed before use. Onasemnogene abeparvovec must only be used in the thawed state.
- For packaging configurations containing up to 14 vials the 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 14 vials thawing will be complete from the 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 medicinal product if you notice any particles or discolouration after thawing and prior to administration.
- Once thawed, do not re-freeze the medicinal product.
- After thawing, onasemnogene abeparvovec should be given as soon as possible. Once the dose volume is drawn into the syringe, it must be administered within 8 hours. If the medicinal product is not infused within 8 hours, the vector-containing syringe must be discarded.

Administration of onasemnogene abeparvovec to patients

- To administer onasemnogene abeparvovec, draw the entire dose volume into the syringe. Remove any air in the syringe before administration. The dose is administered as an intravenous infusion through a venous catheter.

Any unused medicinal product or waste material must be disposed of in accordance with local guidelines on handling of biological waste.

Temporary onasemnogene abeparvovec shedding may occur, primarily through bodily waste. Care staff and patient families must be advised of the following instructions for the proper handling of patient bodily fluids and stools:

- 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 stools. These instructions must be followed 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.

Swissmedic number

67529

Pack sizes

Zolgensma solution for infusion: 1 carton containing 2-14 vials adapted to the patient’s body weight [A].
Onasemnogene abeparvovec is supplied in a vial (10 ml, polymer crystal zenith) with stopper (20 mm chlorobutyl rubber) and seal (aluminium, flip-off) with a coloured cap (plastic) in two different 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 body weight (see “Dosage/Administration” and Table 5 below).

Table 5: Carton/kit configurations

Patient body 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

[a] The vial with a nominal concentration of 2 × 10^{13} vg/ml contains an extractable volume of not less than 5.5 ml.
[b] The vial with a nominal concentration of 2 × 10^{13} vg/ml contains an extractable volume of not less than 8.3 ml.

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

June 2021