NOVARTIS

Patient Safety & Pharmacovigilance

Onasemnogene abeparvovec

OAV101

EU Safety Risk Management Plan

Active substance (INN or common name):	Onasemnogene abeparvovec
Product concerned (brand name):	Zolgensma®
Document status:	Final
Version number:	4.0
Data lock point for this RMP:	Post-marketing data: 23-May-2022 Clinical trial data: 12-Nov-2020
Date of final sign off:	15-Apr-2024

Rationale for submitting an updated RMP:

This updated EU Safety Risk Management Plan (RMP) version 4.0 has been prepared to align with label updates regarding hepatotoxicity, transient thrombocytopenia, and thrombotic microangiopathy. The Key safety messages of the Caregiver information guide, in Annex 6, have been updated to extend the likely occurrence of thrombocytopenia from within 2 weeks to 3 weeks of administration. Additionally, the classification of Study AVXS-101-RG-001 was corrected to post-authorization efficacy study (PAES) only, and Annex 4 has been updated to include the simplified updated versions of the follow up questionnaires.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 3.0
Part I	No changes.
Part II	Module SVII.3.1: Updated Table 8-7: "Important identified risk: Hepatotoxicity: Other details", Table 8-9: "Important identified risk: Transient thrombocytopenia: Other details", Table 8-10: "Important identified risk: Thrombotic microangiopathy", and Table 8-14: "Important potential risk: Tumorigenicity due to chromosomal integration" to align with safety label changes.
Part III	Part III.1: Follow up questionnaire renamed from "Dorsal root ganglia" to "Sensory neuronopathies" to align with the changes made in v2.0 of the checklist. Part III.2: Removed Study AVXS-101-RG-001 from "Additional pharmacovigilance activities". Part III.3: Removed Study AVXS-101-RG-001 from "Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization".
Part IV	No changes.
Part V	Part V.3: Removed Study AVXS-101-RG-001 from "Additional pharmacovigilance activities".
Part VI	Part VI.II.B: Removed Study AVXS-101-RG-001 from "Additional pharmacovigilance activities" and updated Table 13-2: "Important identified risk: Hepatotoxicity" and Table 13-3: "Important identified risk: Transient thrombocytopenia" to align with the above changes and safety label changes.
Part VII	Annex 4: Updated with simplified follow up questionnaires. Annex 6: Updated Caregiver information guide key safety messages to reflect occurrence of thrombocytopenia within 3 weeks of administration.

Other RMP versions under evaluation

No RMPs are currently under evaluation.

Details of the currently approved RMP:

Version number: 3.0

Approved with procedure: EMEA/H/C/004750/II/0040

Date of approval: 14-Sep-2023

QPPV name: Dr Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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AAV	Adeno-associated virus
AAV9	Adeno-associated virus serotype 9
AAVS1	Adeno-associated virus integration site 1
AESI	Adverse events of special interest
ALF	Acute liver failure
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced therapy medicinal product
CCIT	Container closure integrity testing
CK-MB	Creatine kinase isoenzyme - muscle/brain
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CZ	Crystal Zenith
DLP	Data lock point
ddPCR	Droplet digital polymerase chain reaction
DNA	Deoxyribonucleic acid
DRG	Dorsal root ganglia
ECG	Electrocardiogram
HIV	Human immunodeficiency virus
HLT	High level term
INN	International non-proprietary name
LTFU	Long-term-follow up
NCH	Nationwide Children's Hospital
PL	Package leaflet
QPPV	Qualified person for pharmacovigilance
rAAV	Recombinant AAV
RNA	Ribonucleic acid
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
CCI	*CCI*
TMA	Thrombotic microangiopathy
vg	Vector genome

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Onasemnogene abeparvovec Deoxyribonucleic acid (DNA) (synthetic adeno-associated virus 9 vector (AAV9) human survival motor neuron (SMN) protein-specifying)
Pharmacotherapeutic group (ATC Code)	Other drugs for disorders of the musculo-skeletal system (M09AX09)
Marketing Authorization Holder	Novartis Europharm Limited (formerly known as AveXis EU Limited and Novartis Gene Therapies EU Limited)
Medicinal product to which this RMP refers	Onasemnogene abeparvovec
Invented name in the European Economic Area (EEA)	Zolgensma®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Not applicable, as this is a gene replacement therapy.
	Summary of mode of action: Onasemnogene abeparvovec is a gene replacement therapy designed to address the monogenic root cause of SMA via a single dose by replacing the defective primary SMN gene. Approximately 95% of SMA cases are due to bi-allelic deletions to SMN1 gene on chromosome 5q13 with the remainder of cases attributed to deletion on one allele and a point mutation on the second allele. By replacing the defective primary SMN gene with a single administration, onasemnogene abeparvovec increases SMN protein expression in motor neurons and prevents neuronal cell death leading to improved neuronal and muscular function. In transgenic animal models of SMA, i.v. injections of AAV9 led to early and persistent transgene expression and improvement in survival and motor function. Onasemnogene abeparvovec utilizes a non-replicating, recombinant AAV9 capsid to deliver a stable, fully functional human SMN transgene. The ability of the AAV9 capsid to cross the blood brain barrier has been demonstrated. It is not known whether onasemnogene abeparvovec DNA integrates into the patients' genome, although it is designed to reside as a DNA episome in the nucleus of transduced cells. The AAV9 virus is not known to cause disease in humans. The DNA from the wild type AAV9 has been removed and replaced with a promoter and SMN gene. The transgene is introduced to target cells as a self-complementary double stranded molecule. The transgene is activated by a continuous promoter (cytomegalovirus enhanced chicken β actin hybrid), which enables continuous and sustained SMN protein expression.
	Important information about its composition: Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human SMN protein. It is a non-replicating recombinant

	AAV9 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.
Hyperlink to the Product Information	[Proposed SmPC]
Indications in the EEA	**Current**: Zolgensma is indicated for the treatment of: • Patients with 5q 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.
	Proposed: Not applicable
Dosage in the EEA	**Current**: For patients who weigh 2.6 to 21.0 kg: The intravenous dosage is determined by patient body weight with a nominal recommended dose of 1.1×10^{14} vg/kg. An immune response to the AAV9 capsid will occur after administration of onasemnogene abeparvovec, thus patients should not be re-dosed with onasemnogene abeparvovec. Onasemnogene abeparvovec is for a single treatment only.
	Proposed: Not applicable
Pharmaceutical form and strengths	**Current**: Solution for infusion. When thawed, onasemnogene abeparvovec is a clear to slightly opaque, colourless to faint white solution. Each vial contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vg/mL. Vials contain an extractable volume of not less than either 5.5 mL or 8.3 mL. The total number of vials and combination of fill volumes in each finished pack will be customised to meet dosing requirements for individual patients depending on their weight.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

Zolgensma is indicated for the treatment of:

- Patients with 5q 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

The term SMA is applied to a diverse group of genetic disorders, all of which affect the spinal motor neuron (Arnold et al 2015). The most common form of SMA results from bi-allelic mutations to the SMN1 gene on chromosome 5q13 (5q SMA); of these 5q SMA cases, 95% are due to bi-allelic deletions, with the remainder being hemizygous deletions with a point mutation on the other chromosome. Individuals with SMA lack a normally functioning SMN1 gene and are thus dependent on their SMN2 gene expression, however inefficient, to produce the SMN protein necessary for survival (Kolb, Kissel 2011). Deficiency of SMN protein correlates directly with death of the individual's motor neurons. Several phenotypes of SMA are currently recognized based on maximal motor function achieved (Munsat, Davies 1992, Wang et al 2007), with the phenotypes ranging from extremely severe disease symptoms manifesting in utero (Type 0) to less severe symptoms with onset during later life (Type 4) (Kolb, Kissel 2011, Finkel et al 2014, Awano et al 2014).

Incidence:

Publications on SMA indicate that, globally, birth incidence is approximately 1 in 5,000 to 1 in 11,000 live births (Finkel et al 2017, Kolb, Kissel 2015, Lopez-Bastida et al 2017, Tisdale, Pellizzoni 2015). Verhaart et al report that the median incidence of SMA in Europe in the period 2011-2015 was 11.9 per 100,000 births based on a survey of European laboratories (Verhaart et al 2017).

The 2015 incidence reported by Verhaart et al (Verhaart et al 2017) has been used to estimate the 2016 prevalence rate by multiplying the incidence rate with the reported average survival of each SMA type (i.e. prevalence rate = incidence rate × duration).

Based on the Jan-2016 EEA number of live births of 5,211,464 (Eurostat Accessed 16-Jul-2018), the incidence of approximately 620 cases of SMA would be diagnosed.

Recent prevalence data from Orphanet indicate that there is little difference in prevalence between Types 1 and 2, and both types are more prevalent than Types 3 and 4 (Table 2-1).

Table 2-1 SMA Prevalence Rates from Orphanet

SMA Type	Orphanet code	Orphanet rare disease prevalence* Mar-2016	Rare disease prevalence per 10,000 Mar-2016
1	ORPHA83330	1 / 80,000	0.125

SMA Type	Orphanet code	Orphanet rare disease prevalence* Mar-2016	Rare disease prevalence per 10,000 Mar-2016
2	ORPHA83418	1 / 70,000	0.142
3	ORPHA83419	1 / 375,000	0.027
4	ORPHA83420	1 / 300,000	0.033

*Orphanet

Prevalence:

The review of current literature suggests a prevalence range of between 0.1 and 0.7 per 10,000; the birth incidence suggests an estimated prevalence of approximately 0.2 per 10,000 and an estimated calculated prevalence from carrier frequency studies of 0.2 to 0.44 per 10,000.

Considering the updated information available since the 2015 designation application, the Sponsor estimates that the prevalence of SMA has not changed significantly and remains at the 'lower than 0.4 per 10,000' value arrived at following the completion of the Committee for Orphan Medicinal products review at that time. The current estimated prevalence is therefore concluded as: < 0.4 per 10,000 head of population.

Based on the currently published European population of 517,157,147 (Eurostat 2018), the Orphan Condition of SMA is estimated to affect < 20,686 individuals in the community.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age:

Type 0 SMA is extremely rare and is usually fatal in utero or shortly after birth; children with this form of SMA commonly have severe cardiac and brain abnormalities in addition to profound muscle weakness and atrophy and, thus, rarely survive beyond a few months of life (Grotto et al 2016). Following live birth, Type 1 SMA is the most severe infant form.

Type 2 is an intermediate form affecting toddlers; Type 3 is a less severe juvenile form; and Type 4 is a rare, usually adult-onset form of SMA (Table 2-2).

Table 2-2 SMA Classification

Type	Age at symptom onset		Maximum motor function	Life expectancy	SMN2 copy number
0	Fetal		Nil	Days - weeks	1
1	< 6 months	1A: Birth – 2 weeks 1B: < 3 months 1C: > 3 months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 months		Never walks	20 – 40 years	2, **3**, 4
3	1.5 – 10 years	3A: < 3 years 3B: > 3 years	Walks, regression	Normal	3, **4**, 5
4	> 35 years		Slow decline	Normal	4-8

Source: Adapted from Kolb and Kissel 2011.

Type	Age at symptom onset	Maximum motor function	Life expectancy	SMN2 copy number

Bold = predominant SMN2 copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

Gender:

Males are more commonly affected with SMA than females. The male-to-female ratio is 2:1 (Pearn 1973).

Racial and/or ethnic origin:

The SMN1 mutations are pan-ethnic and SMA is seen amongst all ethnic groups. Carrier frequency as determined by quantitative analysis of SMN1 copies varies widely between different populations. Figures of 1 in 47-72 are reported in the US (Sugarman et al 2012), 1 in 41 in Australia (Lawton et al 2015), 1 in 50-80 in Europe and 1 in 20-57 in the Middle East (Lyahyai et al 2012, Zlotogora et al 2016). Caucasians and Ashkenazi Jews have higher carrier rates than Asians, African Americans and Hispanics (Hendrickson et al 2009). Across the world, the extremes of prevalence currently range from 1 in 8 among Hutterites to 1 in 209 among Malians (SMA Europe).

Risk factors:

All forms of SMA are autosomal recessive in inheritance caused by deletion or mutation of the SMN1 gene. As mentioned above Caucasians and Ashkenazi Jews have higher carrier rates than Asians, African Americans and Hispanics.

Main existing treatment options:

There are limited treatment options for patients with SMA. The US FDA (in 2016) and EMA (in 2017) have approved Spinraza™ (nusinersen) for the treatment of SMA. Nusinersen is an antisense oligonucleotide drug designed to increase the production of the SMN protein by modulating the splicing of the SMN2 gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some promise in improving motor function; however, the treatment must be administered indefinitely every 4 months via i.t. injection, requires a lengthy induction period prior to maintenance dosing, and has safety considerations which require clinical monitoring. Coagulation abnormalities/thrombocytopenia and renal toxicity are effects of some oligonucleotides. In analyses of the sham-controlled study of nusinersen included in the FDA Medical Review, the incidences of thrombocytopenia and proteinuria (33% vs. 20%) were higher among nusinersen-treated versus control patients, and 3% (5/173) of all nusinersen-treated patients had 6 events that were hemorrhagic complications of lumbar puncture. In addition, a recent update to the Spinraza SmPC has noted that among patients treated with Spinraza, complications associated with lumbar puncture including serious infection, such as meningitis, have been observed. In addition, hydrocephalus not related to meningitis or bleeding has been reported after DLP in patients, including children, treated with Spinraza (Spinraza SmPC).

The US FDA (in 2020) and EMA (in 2021) have also approved Evrysdi™ (risdiplam) for the treatment of SMA. Evrysdi is indicated for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of Type 1, Type 2 or Type 3 SMA or with one to four SMN2 copies. Evrysdi is taken orally once a day after a meal at approximately the same time

each day. Risdiplam is an SMN2 pre-mRNA splicing modifier designed to treat SMA caused by mutations of the SMN1 gene in chromosome 5q that lead to SMN protein deficiency. Results from two clinical studies, one investigating the effects of Evrysdi on patients with infantile-onset SMA and the other on later-onset SMA, show beneficial effects in very young patients in terms of their motor development and survival at 12 months, compared to data on the natural course of the disease in these patients. The effect in later-onset SMA (Type 2 and 3) has been investigated in a double-blind placebo-controlled trial, including patients between 2 and 25 years of age. In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (48.4%), rash (27.4%) and diarrhea (16.1%). In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (21.7%), headache (20.0%), diarrhea (16.7%), and rash (16.7%) (Evrysdi SmPC).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

SMA is conventionally classified into four phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset spinal muscular atrophy (Kolb and Kissel 2011).

SMA Type 1, the most severe form of SMA, is characterized by rapid motor neuron loss and consequent muscle weakness and paralysis that results in death or the need for permanent ventilation support (a surrogate for death used in studies of this patient population) by 20 months of age in 92% of patients and by 13.6 months of age in 75% of patients (Finkel et al 2014). Furthermore, bulbar weakness in SMA Type 1 patients leads to impaired swallowing, malnutrition and growth failure with natural history suggesting a median age to the need for nutritional support of 8 months of age (Sproule et al 2012). Additionally, these children will never achieve basic key development milestones such as sitting, rolling or maintaining head control and purposeful use of hands for activities such as feeding.

The natural history of disease suggests that motor neurons are lost early, with an onset of loss in the first six months of life in SMA Type 1. Once motor neurons are lost, the prognosis is essentially inexorably progressive and fatal for SMA Type 1 patients (Swoboda et al 2005).

The natural history of SMA Type 1 has been studied in 2 recent multicentre prospective trials in patients with genetically confirmed SMA in the US (Finkel et al 2014, Kolb et al 2016). Although there remains considerable variance in practice related to the manner, degree, and timing of initiation of ventilatory and nutritional support across regions and countries (with some advocating more or less intervention in support of affected infants), it remains clearly established and universally appreciated that, without an effective disease-modifying therapy, progression to death or a state of complete dependence on mechanical ventilatory and nutritional support is universal for those with SMA Type 1 (Ioos et al 2004), particularly those with 2 copies of SMN2.

For patients with SMA Types 2 and 3, the natural history experience describes a slower disease course, but one marked by significant accumulating morbidity. As noted previously, children with SMA Type 2 are thought to have a significantly reduced life expectancy, with death occurring in the third decade of life, in conjunction with considerable morbidity related to

progressive muscle atrophy, weakness, loss of function, development of worsening contractures, and spine curvature with resulting impact on toileting, mobility, transfers and dressing, skin breakdown, and pulmonary function (with the latter leading to ultimate mortality). For patients with SMA Type 3, although life expectancy is thought to be approximately normal, considerable disability is the norm, with a majority of patients ultimately becoming wheelchair dependent at some point in their life. This is particularly true for patients with disease onset before 3 years of age (SMA Type 3a), for whom a majority will lose the previously attained ability to walk within 15 years of symptom onset, with many losing ambulation before 10 years of age (Zerres and Rudnik-Schoneborn 1995, Zerres et al 1997). In longitudinal natural history studies of SMA, patients with Types 2 and 3 SMA, after the initial presentation of the disease, experience slow progressive worsening of function over time, with a large population of ambulatory and non-ambulatory patients experiencing a slow but accumulating annual decline in motor function, as measured by the Hammersmith Functional Motor Scale Expanded, a motor function scale used widely in the study of patients with SMA (Mercuri et al 2016).

Important co-morbidities:

Respiratory compromise is the major cause of morbidity and mortality in SMA. SMA patients may have impaired ability to cough (resulting in poor clearance of lower airway secretions), hypoventilation during sleep, chest wall and lung underdevelopment, and recurrent infections that exacerbate muscle weakness and the integrity of the lung parenchyma. Ventilatory support can range from non-invasive ventilation to invasive ventilation (e.g., tracheostomy tube). In addition, children with SMA may have difficulty eating due to weak swallowing muscles and poor head control, putting them at risk of aspiration and poor nutrition. Feeding tubes (nasojejunal, nasogastric, and gastrostomy) may be an option for children with insufficient caloric intake or impaired oral feeding.

Due to its invasive and physiologically critical nature, tracheostomy placement can be associated with significant morbidity and even mortality. Complications of tracheostomy may include pneumothorax, bleeding and infections. Complications of gastrostomy tube placement may be minor (wound infection, minor bleeding) or major (necrotizing fasciitis, colocutaneous fistula).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Since onasemnogene abeparvovec is intended to be administered as a single i.v. dose in very young or neonatal patients, the toxicology program focused on dosing in neonatal mice and juvenile or neonatal primates.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including:	
Single-dose Toxicity The 12-week i.v. toxicity pivotal studies in neonatal mice (CRL 20122446 and COV 8384031) tested doses ranging from 7.9 E13 to 3.9 E14 vg/kg. Dose and test-article related mortality in mice was observed at doses ≥ 2.4 E14 vg/kg. When a cause of death could be ascribed, mortality was associated with treatment-related atrial thrombosis. The main target organs of toxicity were identified as the heart and liver in mice. Heart related findings: In the ventricular myocardium of mice following i.v. administration, varying terms were used to describe slight to mild mononuclear cell inflammation accompanied by edema, slight to mild fibrosis, and with features of scattered myocardial degeneration/regeneration. This finding was dose-related, present at a high incidence and at all doses and time points up to 12 weeks, and showed evidence of maturation and partial recovery from weeks 3 to 12. Similar findings were occasionally observed in the atrial myocardium of treated mice, but the dominant atrial finding was atrial thrombosis. Atrial thrombi ranged from small to large and with variable features of chronicity and were observed in both unscheduled and scheduled sacrifice animals and doses of ≥ 2.4 E14 vg/kg. When present in unscheduled sacrifice animals, atrial thrombi were typically ascribed as the cause of death. On this basis, the Maximum Tolerated Dose was defined as 1.5 E14 vg/kg, providing a safety margin of approximately 1.4 fold relative to the recommended clinical dose of 1.1 E14 vg/kg. In primates, mixed cell infiltrate and minimal	All patients enrolled in Study AVXS-101-CL-101 had elevated CK isoenzyme - muscle/brain (CK-MB) levels at baseline and at the majority of assessments during the study; however, none of the elevations in CK-MB were considered clinically significant. 8 of 15 patients (53.3%) had elevations in cardiac troponin I levels. Of these 8 patients, 2 (25.0%) had elevated cardiac troponin I levels prior to administration of onasemnogene abeparvovec. None of the elevations in cardiac troponin I observed during the study were considered clinically significant by the investigator. By the end of the study all values had either returned to within the normal range or no longer met the pre-defined criterion for clinical significance. Similarly, in studies AVXS-101-CL-303 and AVXS-101-CL-304, most patients had CK-MB values elevated above the ULN prior to administration of onasemnogene abeparvovec and none were considered clinically significant by the Investigators. Of note, studies of cardiac troponin I levels in healthy newborn infants have indicated that the upper reference limit for cardiac troponin I in this population is considerably higher than the upper reference limit in adult populations (El Khuffash, Molloy 2008). A study of 869 healthy infants defined the upper reference limit for cardiac troponin I in healthy term newborns as 0.183 µg/L (Baum et al 2004). None of the subjects in Study AVXS-101-CL-101 had cardiac troponin I levels exceeding this value. In an additional observational study, data obtained from 357 healthy pediatric subjects aged 0 to 18 years indicated that cardiac troponin I plasma levels were highest in the first month of life, followed by a progressive decline thereafter (Caselli et al 2016). In this observational study, the 95th percentile for cardiac troponin I in newborns ≤1 month of age was 139.36 ng/L (0.139 µg/L). In Study AVXS-101-CL-101, only one subject had a cardiac troponin I level of 0.176 µg/L at Week 1 which transiently exceeded this value. In post-marketing surveillance, elevated troponin is the most commonly reported adverse event without recognizable clinical relevance. Cardiac adverse events are considered an important potential risk.

Key Safety findings (from non-clinical studies)	Relevance to human usage
hemorrhage of the right atrium is the only heart-related finding observed in 1 animal after i.t. administration of onasemnogene abeparvovec at 3 E13 vg/animal. However, in situ hybridization of heart tissue from this animal did not support a direct role for onasemnogene abeparvovec in the observed microscopic findings.	
Liver related findings Onasemnogene abeparvovec-related liver findings in mice included dose-related hepatocellular hypertrophy/regeneration, and less frequently individual cell hepatocellular necrosis, hepatocellular perinuclear vacuolization, and occasionally increased numbers of Kupffer cells. Findings in the liver were sometimes accompanied by modest liver enzyme increases which were partially reversible showing progressively reduced incidence/severity over time. The No Effect Level for test-article related liver findings was 7.9 E13 vg/kg in mice. In cynomolgus monkeys, onasemnogene abeparvovec-related liver findings were observed after i.t. and i.v. administration at doses of ≥ 3 E13 vg/animal and 1.1 E14 vg/kg, respectively, at 6 weeks post administration. The findings consisted of minimal single cell hepatocyte necrosis associated with slight mononuclear cell infiltrates and oval cell hyperplasia after i.t. administration, and oval cell hyperplasia after i.v. administration. These findings correlated with transient, increased aminotransferase activity (alanine and aspartate) at doses of onasemnogene abeparvovec ≥ 3 E13 vg/animal following i.t. administration or 1.1 E14 vg/kg following i.v. administration. After long-term observation (12- and 6-months) following i.t. and i.v. administration, respectively, these liver findings (single cell necrosis of hepatocytes and oval cell hyperplasia), demonstrated partial (i.v.) or complete (i.t.) reversibility.	TEAEs of elevated transaminases occurred in 26.7% of patients in AVXS-101-CL-101, 9.1% in AVXS-101-CL-303, and 14.3% in AVXS-101-CL-304. None of these elevations were associated with clinical symptoms. In the post-marketing setting, cases of ALF have been reported some of which had fatal outcomes. Hepatotoxicity is an important identified risk.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Dorsal root ganglia In cynomolgus monkeys, i.t. and i.v. administration of onasemnogene abeparvovec has been associated with clinically silent (asymptomatic) microscopic changes in the CNS and/or peripheral nervous system at up to 6 weeks post administration. These microscopic findings were noted without a dose relationship in the DRG, trigeminal ganglia, spinal cord, dorsal spinal nerve roots, and peripheral nerves at 6 weeks post-dose. The findings in the DRG (at all levels) and/or trigeminal ganglia included mononuclear cell inflammation, neuronal degeneration, satellitosis, and/or neuronal necrosis. In the spinal cord, microscopic findings included axon degeneration in the dorsal, ventral and/or ventrolateral funiculi, and gliosis in the spinal cord (dorsal funiculus). In the peripheral nerves, microscopic findings consisted of an increased incidence and/or severity (relative to controls) of minimal or slight axonal degeneration observed only after i.t. administration. Axonal degeneration and related findings in the spinal cord, spinal nerve roots and peripheral nerves was considered secondary to neuronal degeneration in the DRG. After 6- and 12-months of observation following i.v. and i.t. administration, respectively, the microscopic findings in DRG/trigeminal ganglia were considered non-progressive due to a decrease in the incidence, severity, and/or distribution of the DRG/trigeminal ganglia findings compared with findings at 6 weeks post-dose. • Six-months after i.v. administration of onasemnogene abeparvovec at 1.1 E14 vg/kg, the microscopic findings of neuronal degeneration and mononuclear cell inflammation noted at 6 weeks post-dose were still present in the DRG, but considered resolving and/or non-progressive in the DRG and resolved in the trigeminal ganglia due to decreased incidence and severity.	The etiology of DRG inflammation is complex and not well understood. DRG-related sensory abnormalities have not been observed in humans who received i.v. or i.t. onasemnogene abeparvovec. Hence, the relevance of these inflammatory changes in primate DRG without steroid treatment to a clinical DRG syndrome in humans treated with steroids has not been established (Hordeaux et al 2020). DRG toxicity is an important potential risk.

Key Safety findings (from non-clinical studies)	Relevance to human usage
• At 12 months following i.t. administration, onasemnogene abeparvovec (not indicated for use) related findings in the DRG and/or trigeminal ganglia were limited to minimal severity neuronal degeneration, mononuclear cell inflammation, and/or satellite glial cell aggregates in animals administered ≥ 1.2 E13 vg/animal. The severity of microscopic findings in the DRG/ trigeminal ganglia was generally decreased compared with that at 6 weeks post-dose, indicating evidence of non-progression and a trend towards resolution of the findings. Resolution of the DRG/trigeminal ganglia finding was almost complete at the 1.2 E13 vg/animal dose, with the exception of neuronal degeneration noted at a decreased incidence and severity in the DRG. The DRG was not identified as a target organ of toxicity in previous onasemnogene abeparvovec studies conducted in mice (intracerebroventricular route of administration). However, in addition to the onasemnogene abeparvovec related DRG findings after i.v. or i.t. administration to cynomolgus monkeys, similar findings have been reported after administration of AAV9 vectors in rhesus macaques and mini-pigs (Hinderer et al 2018, Hordeaux et al 2018).	
Repeat-dose toxicity No repeat-dose toxicity studies were performed with onasemnogene abeparvovec as onasemnogene abeparvovec is only intended for single dose administration.	Not applicable
Reproductive/developmental toxicity No reproductive or developmental toxicity studies were performed with onasemnogene abeparvovec since these studies are not relevant for the product or clinical population.	Not applicable
Genotoxicity and carcinogenicity	The long-term persistence of gene expression reported for recombinant AAV vectors is believed to be due to maintenance of episomes that over months are converted into higher molecular weight

Key Safety findings (from non-clinical studies)	Relevance to human usage
No genotoxicity and carcinogenicity studies were performed with onasemnogene abeparvovec as these studies are generally not required for gene therapy vectors.	concatemerized genomes that do not integrate into the host chromosomes but assimilate with chromatin with a typical nucleosomal pattern (Balakrishnan and Jayandharan 2014). Since the onasemnogene abeparvovec product uses AAV9 with all the wild-type DNA removed from the capsids, except for the Inverted Terminal Repeats, the potential risk of incorporation of onasemnogene abeparvovec into the patient chromosomal DNA is thought to be significantly reduced. Although onasemnogene abeparvovec is not anticipated to integrate into the host cell genome, the long-term consequences of administering AAV viral vectors to humans are not yet fully understood. Although rare, there have been reports of rAAV vector integration into animal model genomes with subsequent genotoxicities (Nakai et al 2003; Chandler et al 2017, Zhong et al 2013). Only one paper was identified that reported tumours in an animal model in which an AAV9 vector was administered (Walia et al 2015). This group evaluated the efficacy of a single i.v. injection of rAAV9 expressing the mouse Hexb cDNA (AAV9-HexB) in an SD mouse model. The authors cited similar findings have been reported in mice treated neonatally for β-glucuronidase and as 9- to 11-week-old adults for ornithine transcarbamylase deficiencies, which were attributed to insertional mutagenesis by the AAV vectors which integrated, in some of the tumours, within a 6-kb window on chromosome 12, near the Rian and Mirg genes. AAV genome sequences have been found in human hepatocellular carcinoma samples near known cancer driver genes, although at a low frequency (Nault et al 2015). The case for the association of rAAV vectors with cancer in humans is not compelling, given that at least five different serotypes, AAV1, AAV2, AAV5, AAV8, and AAV9, have been, or are currently being used, in 162 Phase I/II, and one Phase III clinical trials in humans to date, and no adverse events, much less cancer of any type, have ever been observed or reported. Overall, the tumourigenic potential of rAAV vectors appears to be minimal, and this is likely to be particularly true in tissues that divide relatively slowly or are non-dividing such as neurons. Nevertheless, the potential long-term risk for carcinogenicity is not known since there is a paucity of long-term data. Prolonged expression of the transgene may also be associated with long-term risks resulting from unregulated cell growth and malignant transformation. In recognition of these potential risks, Novartis has instituted long-term-follow up (LTFU) studies which include long-term safety evaluation for “delayed” adverse events as a consequence of persistent biological activity of the genetic material or other components of the products used to carry the genetic material. These events have been classified as adverse events of special interest (AESI) in our LTFU studies and specifically include the occurrence of new malignancies or tumors (Protocol Number: AVXS-101-LT-001, Version 5.0, Amendment 4, 30-Oct-2020; Protocol Number: AVXS-101-LT-002, Version 4.0, Amendment 3, 15-Oct-2020). The study plan calls for scheduled visits with a health care provider to elicit and record new findings for each study subject, including history, physical examination, or laboratory testing at minimum intervals of one year to record the emergence of new clinical conditions, including new malignancy(ies). In addition, a detailed record of all exposures to mutagenic agents and other medicinal products is specifically maintained. There are 13 patients currently being followed in study LT-001 who have follow-up ranging from 59.8 - 79.2 months from the time of gene therapy (as of

Key Safety findings (from non-clinical studies)	Relevance to human usage
	12-Nov-2020). As of 12-Nov-2020, 31 patients were being followed in study LT-002 with ages ranging from 19.2 to 73.1 months. In the i.v. cohort in LT-002 (n=23), mean (range) age at data cut-off for age at start of LT-002 was 2.3 (1.6–2.7) years; mean (range) time since dosing with onasemnogene abeparvovec was 2.4 (1.8–2.8) years. In the i.t. CCI Patients in both long-term studies will be monitored annually for 15 years from gene therapy administration.
Other toxicity-related information or data	
Some mice affected with a form of SMA Type 1 that were treated with the study vector developed localized vascular necrosis around the ear called necrotic pinna. This is believed to be unrelated to the vector, and likely related to an underlying defect that has been observed to occur in several SMA mouse models (Narver et al 2008).	Ear lobe necrosis was reported as a non-serious adverse event in patient 028-002. No ear lobe necrosis was reported in any other clinical studies (data on file). A search of the onasemnogene abeparvovec safety database for all similar events was conducted through 28-Feb-2021, using MedDRA PTs found in MedDRA high level group term External ear disorders (excluding congenital) [10015732], HLT Necrosis NEC [10028882], and HLT Non-site-specific necrosis and vascular insufficiency NEC [10029558]. No similar events were reported for onasemnogene abeparvovec. One alternative explanation for the ear lobe necrosis seen in onasemnogene abeparvovec study CL-302 patient 028-002 is the potential effects of intensive care unit practices, including taping/securing of devices or tubing to the ears of patients. Though there is no information confirming such actions in patient 028-002, these procedures are quite common in persons treated in intensive care units. The ear lobe necrosis observed in patient 028-002 in study CL-302 is considered to be unlikely related to treatment with onasemnogene abeparvovec, but more likely to other factors, including potential autonomic dysfunction and associated vascular perfusion abnormalities. There have been 2 publications regarding patients with Type I SMA who developed digital necrosis (Araujo et al 2009, Rudnik-Schoneborn et al 2010). The first of these described 2 infants who developed digital discoloration/necrosis involving hands and feet at 4 months of age7. Lesions eventually healed over a period of 3-10 months. One child had 2 copies of the SMN2 gene, but copy number is unknown in the other. A second publication described 2 patients with Type I SMA who both had only 1 copy of the SMN2 gene (Rudnik-Schoneborn et al 2010). One patient developed necrosis of hand digits at 4 months of age, with biopsy at 6 months showing necrosis of epidermis and upper dermis, and thrombotic occlusion of small vessels. The second patient developed necrosis of toes at age 3 months. Skin biopsy showed non-specific vasculitis without structural defects of the dermis. Both patients eventually expired. Neither of these publications described necrosis of ears. The authors of these publications agreed that autonomic dysfunction is most likely the primary source of vascular perfusion abnormalities in SMA. Investigations by a third group (Arai et al 2005) in a small cohort of children with various types of SMA documented autonomic abnormalities in a number of those studied, including 3 cases of Type I SMA, lending support to this view.

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
	The data described in non-clinical studies and in patient case reports indicate that necrosis of peripheral tissues, including digits, ears, and tails of SMA mice, and digits of some cases of human SMA, may be observed in animal models of and humans with this genetic disorder. This has been seen in SMA mice in which experimental treatments have been investigated, including onasemnogene abeparvovec, as well as other treatments, and in such animals not receiving treatment. Necrosis of the digits of the hands and feet has been rarely reported in humans with severe Type I SMA not receiving disease-specific treatment. The authors of a number of these reports suggest that autonomic dysfunction with associated vascular perfusion abnormalities is the primary cause of these pathological findings. However, the etiology is not yet known with certainty.
Both mice and monkeys generated an immune response against the AAV9 (adeno-associated virus serotype 9) capsid.	Given the single dose nature of the treatment paradigm, there is no data to suggest that these antibodies were neutralizing or impacted onasemnogene abeparvovec levels. Antibodies generated against human SMN (survival motor neuron) in nonhuman primates appeared to be species specific but were not formally tested for neutralization as they did not appear to impact or limit efficacy in the animal disease models tested. Production of an anti-AAV9 response would be a more critical issue for a repeat-dose therapy relative to the established single dose paradigm leveraged for most AAV vector therapies, and multiple or repeat dose paradigms are currently not being considered for onasemnogene abeparvovec.

Conclusions from non-clinical data:

- Important identified risks from pre-clinical studies include: hepatotoxicity.
- Important potential risks from pre-clinical studies include: cardiac adverse events and DRG toxicity.
- There is no missing information identified from pre-clinical studies.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

The first-in-human clinical trial of onasemnogene abeparvovec was completed (AVXS-101-CL-101). The Phase 1 study began in Apr-2014 in the US and completed enrolment of 15 patients in Dec-2015. The trial was a Phase 1 study evaluating safety and efficacy of onasemnogene abeparvovec gene transfer in SMA Type 1 patients genetically tested to confirm no functional copies of SMN1 and 2 copies of SMN2. There was one patient who was dosed beyond 6 months of age whilst the remaining patients were dosed at 6 months or less.

Two cohorts were dosed:

- Cohort 1: enrolled 3 patients who were administered 3.7×10^{13} vg/kg i.v.;
- Cohort 2: enrolled 12 patients who were administered 1.1×10^{14} vg/kg i.v.

The onasemnogene abeparvovec drug product used in the Nationwide Children's Hospital (NCH) Phase 1 study (AVXS-101-CL-101) was manufactured by NCH. In the NCH Phase 1 study, all patients were treated with the same lot of IMP and there were 2 doses assessed in this dose escalation study. The IMP lot used in the Phase 1 study was directly measured by a validated/more precise ddPCR method and the Cohort 2 dose was determined to be 1.1 E14 vg/kg. The Cohort 2 dose is the proposed therapeutic dose. The therapeutic i.v. dose of onasemnogene abeparvovec used in all other studies is determined by the ddPCR assay and is 1.1 E14 vg/kg.

All 15 treated patients completed the study at 24 months of follow-up after dosing and are included in the Safety Analysis Set: 13 of these patients were enrolled in Study AVXS-101-LT-001 as of DLP. Patients completing the Phase 1 study are being followed for 15 years, as part of a separate long-term follow-up study (AVXS-101-LT-001).

Onasemnogene abeparvovec has been administered intravenously in 4 Novartis-sponsored clinical studies. As of 12-Nov-2020, a total of 97 patients have been exposed in these clinical trials. CCI [redacted] Intravenous administration exposure is presented in Table 4-1.

Table 4-1 Intravenous administration in clinical trials

		Study CL-101			Study CL-302	Study CL-303	Study CL-304	Therapeutic i.v. dose (N=97)†
	Statistic	Low Dose (N=3)	Proposed therapeutic dose (N=12)	All (N=15)	1.1 E14 vg/kg (N=33)	1.1 E14 vg/kg (N=22)	1.1 E14 vg/kg (N=30)	
Actual Dose Administered (vg)	n	3	12	15	27	22	18	79
	Mean	4.467	11.333	9.960	6.502	6.442	4.214	6.698
	Standard deviation	0.3868	2.4618	3.5870	1.1609	1.1833	0.5886	2.5529
	Median	4.690	11.000	10.000	6.060	6.601	4.125	6.068
	Minimum	4.02	8.00	4.02	4.96	4.39	3.30	3.30
	Maximum	4.69	16.00	16.00	9.36	8.40	5.51	16.00
Compliance (%)	n	3	12	15	27	22	18	79
	Mean	100.00	100.00	100.00	102.48	100.49	98.67	100.68
	Standard deviation	0.000	0.000	0.000	3.608	4.641	8.681	5.357
	Median	100.00	100.00	100.00	102.04	101.17	96.87	100.00
	Minimum	100.0	100.0	100.0	95.9	89.7	88.0	88.0
	Maximum	100.0	100.0	100.0	109.9	110.4	122.6	122.6
Total Volume Administered (mL)	n	3	12	15	33	22	30	97
	Mean	112.267	96.008	99.260	24.194	17.316	18.113	29.638
	Standard deviation	9.7572	19.9427	19.2718	9.1004	6.5026	5.4708	26.9923

		Study CL-101			Study CL-302	Study CL-303	Study CL-304	Therapeutic i.v. dose (N=97)†
	Statistic	**Low Dose (N=3)**	**Proposed therapeutic dose (N=12)**	**All (N=15)**	**1.1 E14 vg/kg (N=33)**	**1.1 E14 vg/kg (N=22)**	**1.1 E14 vg/kg (N=30)**	
	Median	117.900	92.600	101.000	20.300	16.650	19.750	20.000
	Minimum	101.00	67.30	67.30	12.40	9.00	8.70	8.70
	Maximum	117.90	134.70	134.70	44.00	41.30	25.00	134.70
Duration of Injection (min)	n	3	12	15	33	22	30	97
	Mean	51.0	65.2	62.3	63.7	62.9	60.3	62.7
	Standard deviation	17.32	9.65	12.26	10.86	10.94	4.20	9.19
	Median	61.0	65.0	64.0	60.0	60.0	60.0	60.0
	Minimum	31	40	31	56	30	45	30
	Maximum	61	80	80	115	90	70	115
Injection of entire volume of product								
Yes	n (%)	3 (100.0)	12 (100.0)	15 (100.0)	33 (100.0)	22 (100.0)	30 (100.0)	97 (100.0)
No	n (%)	0	0	0	0	0	0	0
Reason of entire volume was not injected								
Adverse event	n (%)	0	0	0	0	0	0	0
Mechanical/ technical	n (%)	0	0	0	0	0	0	0
Other	n (%)	0	0	0	0	0	0	0

		Study CL-101			Study CL-302	Study CL-303	Study CL-304	Therapeutic i.v. dose (N=97)†
	Statistic	Low Dose (N=3)	Proposed therapeutic dose (N=12)	All (N=15)	1.1 E14 vg/kg (N=33)	1.1 E14 vg/kg (N=22)	1.1 E14 vg/kg (N=30)	
Injection interruption								
Yes	n (%)	0	0	0	4 (12.1)	0	1 (3.3)	5 (5.2)
No	n (%)	3 (100.0)	12 (100.0)	15 (100.0)	29 (87.9)	22 (100.0)	29 (96.7)	92 (94.8)
Reason of injection interruption								
Adverse event		0	0	0	0	0	0	0
Mechanical/ technical		0	0	0	3 (9.1)	0	0	3 (3.1)
Other		0	0	0	1 (3.0)	0	1 (3.3)	2 (2.1)

† Excludes low dose patients

4.1.1 Study AVXS-101-CL-303

AVXS-101-CL-303 (Study CL-303) is a completed (last patient last visit: 12-Nov-2019; complete study report: 31-Mar-2020) Phase 3, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with SMA Type 1 with one or two SMN2 copies in which patients are dosed with 1.1 E14 vg/kg of onasemnogene abeparvovec (Table 4-2). Study enrolment was completed with 22 patients. All treated patients received the full dose of onasemnogene abeparvovec without interruption according to protocol dosing schedule. One death led to premature discontinuation, 1 patient discontinued prematurely due to withdrawal of consent, and 1 patient discontinued due to an adverse event.

Table 4-2 Summary of demographic and baseline characteristics for Study AVXS-101-CL-303 (Safety Population)

Characteristic Category/Statistic	All Patients N = 22
Age at baseline (months)	
Mean (SD)	3.7 (1.60)
Median	3.5
Min, Max	0.5, 5.9
Gender, n (%)	
Female	12 (54.5)
Male	10 (45.5)
Race, n (%)	
White	11 (50.0)
Other	6 (27.3)
Black or African American	3 (13.6)
Asian	2 (9.1)
Ethnicity, n (%)	
Not Hispanic or Latino	18 (81.8)
Hispanic or Latino	4 (18.2)
Weight at baseline (kg)	
Mean (SD)	5.8 (1.05)
Median	5.8
Min, max	3.9, 7.5
Gestational age at birth (weeks)	
Mean (SD)	39.0 (0.95)
Reported swallowing thin liquid, n (%)	
Yes	22 (100)
No	0
Reported feeding support, n (%)	
Yes	0
No	22 (100)
Reported ventilatory support[1], n (%)	
Yes	0
No	22 (100)

Characteristic Category/Statistic	All Patients N = 22

Note: All patients received proposed therapeutic dose (1.1 E14 vg/kg) of onasemnogene abeparvovec intravenously

[1] Ventilatory support = respiratory assistance per day via non-invasive ventilatory support.

4.1.2 Study AVXS-101-CL-304

AVXS-101-CL-304 (Study CL-304) is a completed, global, multicentre, Phase 3, open-label, single-arm study of a single, one-time dose of 1.1 E14 vg/kg onasemnogene abeparvovec administered via i.v. infusion (Table 4-3). Enrolment was closed on 08-Nov-2019.

Table 4-3 Summary of demographic and baseline characteristics for Study AVXS-101–CL-304 (Enrolled Population)

Characteristic Category/Statistic	Number of SMN2 copies		
	2 copies n=14	3 copies n=15	4 copies[a] n=1
Age at baseline[b] (days)			
Mean (SD)	20.6 (7.87)	28.7 (11.68)	36.0
Median (Min, Max)	21 (8, 34)	31 (9, 43)	36 (36, 36)
Gender, n (%)			
Male	4 (28.6)	6 (40.0)	1 (100)
Female	10 (71.4)	9 (60.0)	0
Race, n (%)			
White	7 (50.0)	10 (66.7)	1 (100)
Other	3 (21.4)	2 (13.3)	0
Black or African American	2 (14.3)	0	0
Asian	2 (14.3)	2 (13.3)	0
American Indian or Alaska Native	0	1 (8.3)	0
Ethnicity, n (%)			
Not Hispanic or Latino	10 (71.4)	13 (86.7)	1 (100)
Hispanic or Latino	4 (28.6)	2 (13.3)	0
Weight at baseline (kg)			
Mean (SD)	3.6 (0.39)	4.1 (0.52)	5.0
Gestational age at birth (weeks)			
Mean (SD)	38.2 (1.42)	38.8 (1.47)	39.0
Familial history of SMA including affected siblings or parent carriers, n (%)			
Yes	8 (57.1)	10 (66.7)	1 (100)
No	6 (42.9)	5 (33.3)	0
Siblings affected by SMA, n (%)			
1 Sibling	2 (14.3)	7 (46.7)	0
2 Siblings	4 (28.6)	0	0

Characteristic Category/Statistic	Number of SMN2 copies		
	2 copies n=14	3 copies n=15	4 copies[a] n=1
More Than 3 Siblings	0	1 (6.7)	0
No Siblings Affected	4 (28.6)	5 (33.3)	1 (100)

[a] Enrollment suspended in this cohort.

[b] Age = (dose date – date of birth + 1).

Note: All patients received proposed therapeutic dose (1.1 E14 vg/kg) of onasemnogene abeparvovec intravenously.

4.1.3 Study AVXS-101-CL-302

AVXS-101-CL-302 (Study CL-302) is a completed, Phase 3, open-label, single-arm study of a single, one-time dose of 1.1 E14 vg/kg onasemnogene abeparvovec administered via i.v. infusion conducted in patients with SMA Type 1 (Table 4-4). Enrollment was closed on 21-May-2019.

Table 4-4 Summary of demographic and baseline characteristics for Study AVXS-101-CL-302 (Safety Population)

Characteristic Category/Statistic	Overall N = 33
Age[a] (months)	
Mean (SD)	4.06 (1.28)
Median	4.1
Min, Max	1.8, 6.0
Gender, n (%)	
Female	19 (57.6)
Male	14 (42.4)
Weight at baseline (kg)	
Mean (SD)	5.8 (1.04)
Gestational age at birth (weeks)	
Mean (SD)	39.1 (1.37)
Familial history of SMA including affected siblings or parent carriers, n (%)	
No	32 (97.0)
Yes	1 (3.0)
Reported swallowing thin liquid, n (%)	
Yes	31 (93.9)
No	2 (6.1)
Reported feeding support, n (%)	
Yes	10 (30.3)
No	23 (69.7)
Reported ventilatory support, n (%)	
Yes	9 (27.3)
No	24 (72.7)

Note: All patients received proposed therapeutic dose (1.1 E14 vg/kg) of onasemnogene abeparvovec intravenously.

[a] Age = (Date of Treatment – Date of Birth + 1).

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Active viral infection (includes human immunodeficiency virus (HIV) or serology positive for hepatitis B or C)	These patients were excluded because of the concern that AAV may be a risk for the liver and would affect safety endpoints. Hepatotoxicity is considered an Important Identified Risk for onasemnogene abeparvovec.	No	This population of patients is not considered as missing information because: 1. Taking into account the rarity of SMA, the likelihood of an SMA patient with active viral infection (HIV or serology positive hepatitis B or C) being treated with onasemnogene abeparvovec is small and thus there is limited ability to obtain data on this subset of patients in the post-marketing setting. 2. Even if such patients were treated, taking into account the seriousness of the disease and the potential for onasemnogene abeparvovec to benefit the patient, the benefit-risk would remain positive for these patients who have limited treatment options.
Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at the screening visit • Patients may be managed using non-invasive ventilator support (bi-level positive airway pressure) for less than 16 hours per day at the discretion of their physician or study staff.	Inclusion of these patients would have affected the ability to assess efficacy endpoints in such a small patient population.	No	Use in this patient population is not expected to be associated with additional risks of clinical significance relative to the seriousness of the disease.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Concomitant use of any of the following drugs: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, i.v. immunoglobulin, rituximab).	Drugs used for the treatment of myopathy or neuropathy would have prevented assessment of efficacy endpoints. As patients were treated with steroids prophylactically during the study, patients undergoing immunotherapy would have been at greater risk of immunosuppression with concurrent steroids. Patients on treatment with diabetic agents would have been at risk of poor blood sugar control with concomitant steroids.	No	Although these patients were excluded, in reality the likelihood of a patient suffering SMA Type-1 and being on any of these concomitant treatments is ultra-rare and is not amenable to clinical investigation. For this reason, use in patients taking these medications is not considered to be missing information.
Patients with anti-AAV9 antibody titres > 1:50 as determined by enzyme-linked immunosorbent assay binding immunoassay.	These patients were excluded as there was a risk that antibodies would neutralize the virus and thus would have affected efficacy endpoints.	No	The safety is not expected to be different in this population. The SmPC states that “Patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec”. “An immune response to the adeno associated viral vector serotype 9 (AAV9) capsid will occur after infusion of onasemnogene abeparvovec.”
Abnormal laboratory values considered to be clinically significant (GGT > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, hemoglobin < 8 or > 18 g/dL; white blood cells > 20,000 per cm).	Inclusion of these patients would have affected the safety endpoints of the study.	No	Liver function is monitored following treatment with onasemnogene abeparvovec and patients are given prophylactic prednisolone to minimize the important identified risk of hepatotoxicity. It is possible that these patients may be treated in clinical practice taking into account the otherwise fatal outcome of their disease if untreated. However, investigating such a small subset of patients with abnormal clinically significant laboratory values would not be possible in this ultra-rare disease. Accordingly, use in this patient population is not considered missing information.
Patients with a single base substitution in SMN2 (c.859G>C in exon 7)*	Excluded based on predicted less severe phenotype so that a comparison with the	No	This population of patients is not considered as missing information because:

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	published natural history would be feasible.		1. Taking into account the rarity of patients with a single base substitution in SMN2 (c.859G>C in exon 7) there is limited ability to obtain data on this subset of patients in the post-marketing setting. 2. Even if such patients were treated, taking into account the seriousness of the disease and the potential for onasemnogene abeparvovec to benefit the patient, the benefit-risk would remain positive for these patients who have limited treatment options. 3. The safety profile in these patients is not expected to be different than those participating in the clinical development and hence is not considered to be missing information.

*Excluded from study AVXS-101-CL-101. Such patients have not been excluded in the other planned or ongoing clinical trials. To date, no such patients have been enrolled.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Due to the small number of patients, the clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Elderly population	Not included in the clinical development program
Pediatric population	All patients were infants (age range of 0.3 to 7.9 months)
Pregnant women	
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	

Type of special population	Exposure
• Patients with hepatic impairment • Patients with renal impairment	
Population with relevant different ethnic origin	Clinical trials with onasemnogene abeparvovec included patients that were Caucasian, Black/African American, Hispanic, Asian, and American Indian/Alaska native.
Subpopulations carrying relevant genetic polymorphisms	AVXS-101-CL-101 included patients with proven bi-allelic mutations of the SMN1 gene (diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 2 copies of SMN2). Patients with a single base substitution in SMN2 (c.859G>C in exon 7) were excluded from study AVXS-101-CL-101 in order to allow comparison with published natural history. Such patients are not excluded in the other planned or ongoing clinical trials. AVXS-101-CL-302 and AVXS-101-CL-303 includes patients with biallelic SMN1 mutations (deletion or point mutations) and 1 or 2 copies of SMN2 [inclusive of the known SMN2 gene modifier mutation (c.859G>C)]. AVXS-101-CL-304 includes patients with 2 or 3 copies of SMN2.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Post-authorization data is based on the actual patient exposure because it is used as a single treatment only.

6.1.2 Part II Module SV.1.2. Exposure

The cumulative estimated post-marketing (non-clinical trial) exposure until 23-May-2022 is 2269 patients.

The cumulative post-marketing exposure, distributed by region, is presented in Table 6-1.

Table 6-1 Cumulative exposure from marketing experience

Formulation	EEA	CCI	CCI	ROW
Onasemnogene abeparvovec (i.v.)	588	CCI	CCI	768
CCI				

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

There are no properties of onasemnogene abeparvovec that would make it attractive for misuse for illegal purposes.

7.2 Specific risks of advanced therapy medicinal products

Onasemnogene abeparvovec is manufactured in the US. Product is filled in vials with two fill volumes 5.5 mL and 8.3 mL. The product is stored at or below -60°C. The vials are tested and labelled and shipped frozen to a commercial manufacturing organization in the EEA. Once an order for a patient is received, the number of vials for the patient weight is packed in secondary packaging and QP release occurs. The patient specific pack is transferred into a pre-conditioned CCI shipper packed with dry ice to maintain shipment temperatures ≤ -60°C. The shipper is equipped with temperature probes and a global positioning system tracker. A specialized courier service ensures that the product is cleared through customs and delivered to the hospital pharmacy.

The main risk associated with the logistics of the product is a break in the cold chain.

7.2.1 Shipping validation

Shipping Validation Performance Qualification was performed to confirm that the selected shipper for onasemnogene abeparvovec was able to protect the drug during shipping and assess shipping for climate variations. Onasemnogene abeparvovec Drug Product is filled into 10 mL CZ vials to a nominal volume of either 5.5 or 8.3 mL and frozen at ≤ -60°C. Two carton sizes are available depending on the dose. Small carton holds 2 – 9 vials while the larger carton holds 10 to 14 vials. A single carton is loaded into a pre-conditioned CCI shipper to maintain shipment temperatures ≤ -60°C.

Three shipments were made with onasemnogene abeparvovec Drug Product and onasemnogene abeparvovec Drug Product Surrogate CCI The onasemnogene abeparvovec Drug Product Surrogate consisted of CCI filled into CZ vials at a volume of either 5.5 mL or 8.3 mL. The onasemnogene abeparvovec Drug Product Surrogate was determined to be suitable since it contains all the same excipients except the vector. The vials were examined for container closure integrity testing (CCIT) prior to freezing and packaging and again post-shipment. All vials tested for CCIT met the acceptance criteria. Upon receipt of the package after the respective shipments, the vials of onasemnogene abeparvovec Drug Product and onasemnogene abeparvovec Drug Product Surrogate were placed in ≤ -60 °C until the final quality control took place after all shipments were completed.

All three shipments consisted of CCI, which satisfied the requirement of greater than or equal to CCI The duration of each shipment also met the requirement of being greater than or equal to CCI The shipments were tested by climate variations, pressure, handling practices and security checks as would be used in routine conveyance. The carton configurations were tested by simulating a maximum vial load, in duplicate, and a minimum vial load. The temperature of the onasemnogene abeparvovec Drug Product and onasemnogene

abeparvovec Drug Product Surrogate remained below -60°C for the duration of all three shipments.

Shipping verifications were also executed for both of the EU cartons for summer and winter studies using the CCI shipper along with ISTA 3A testing. The packaging and shipping method have been demonstrated to ensure the selected shipper maintains the product load within the required temperature range and protects the product from damage.

7.2.1.1 Product stress and stability studies

Product stress and stability studies were executed to mitigate potential risk in temperature excursions during shipping and support the planned shipping duration at ≤ -60°C.

To support potential risk in temperature excursions during shipping the onasemnogene abeparvovec material was stressed by performing the following challenges through laboratory studies and during the shipping validation. The results of this process showed no impact to the onasemnogene abeparvovec drug product (Table 7-1). The product stress studies concluded that the quality attributes evaluated remain stable through various temperature excursions.

CCI

7.2.2 Flow-chart of the logistics of the therapy

Not applicable.

7.2.3 Risks to living donors (where applicable)

Not applicable.

7.2.4 Risks to patients in relation to quality characteristics, storage and distribution of the product

Onasemnogene abeparvovec is manufactured and released in GMP environment, using standard techniques and methods well established in the manufacturing of biologics (refer Section 8.1.1 for more details).

7.2.5 Risks to patients related to administration procedures

There is no known toxicity associated with overexpression of the SMN protein. Accidental exposure is estimated to result in very limited local exposure and would not result in significant SMN expression. There were no AEs related to administrative procedures that resulted in irreversible or sustained clinical sequelae (refer Section 8.1.1 for more details).

7.2.6 Risks related to interaction of the product and the patient

Not applicable.

7.2.7 Risks related to scaffolds, matrices and biomaterials

Not applicable.

7.2.8 Risks related to persistence of the product in the patient

Since onasemnogene abeparvovec uses AAV9 with all wild-type DNA removed from the capsids, except for the inverted terminal repeats, the potential risk of incorporation of onasemnogene abeparvovec into patient chromosomal DNA is thought to be significantly reduced (refer Section 8.1.1 for more details).

7.2.9 Risks to healthcare professionals, care givers, offspring and other close contacts with the product or its components, or with patients

There are no adverse consequences of vector shedding reported. The likelihood of recombination is very low, due to the characteristics of the vector and proper control for replication competent viruses. AAV9 distributes to the gonads, albeit at concentrations lower than the distribution to other tissues (refer Section 8.1.1 for more details).

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1 Identification of safety concerns in the initial RMP submission

8.1.1 Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Recognizing that onasemnogene abeparvovec is classified as an ATMP, an overview of ATMP-specific considerations, including risks that are not considered important for inclusion in the list of safety concerns, is provided below.

Table 8-1 Risks not considered important for inclusion in the list of safety concerns

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)
Blood and lymphatic system disorders: Common: lymphocyte count decreased; white blood cell count decreased; white blood cell disorder
Vascular disorders: Common: blood pressure diastolic decreased
Respiratory, thoracic and mediastinal disorders: Common: sleep apnea syndrome
Gastrointestinal disorders: Common: vomiting; diarrhea; dyspepsia
Hepatobiliary disorders: Common: GGT increased; ammonia increased
Renal and urinary disorders: Common: occult blood in urine
Metabolism and nutrition disorders: Common: weight decreased; malnutrition
General disorders and administration site conditions: Common: failure to thrive

Table 8-2 ATMP-specific risks

Risk	Reason for not being an important risk
Accidental self-inoculation	All humans express SMN protein, and there is no known toxicity associated with overexpression of the protein. Accidental exposure is estimated to result in very limited local exposure and would not result in significant SMN expression. The risk of needle-stick injuries is no greater when administering this product compared to any other.
Vector shedding	A shedding study has been conducted in humans, in which onasemnogene abeparvovec was analyzed from urine, stool, and saliva samples of 5 treated patients. All five patients analyzed were dosed i.v. with the proposed therapeutic dose equivalent to 1.1×10^{14} vg/kg. For the analysis of the product, a validated scAAV9-SMN Genomic Titre Assay using ddPCR was utilized. Onasemnogene abeparvovec was detectable in the shed samples from day 1 post injection. Concentrations of the vector shed in saliva and urine were low and below the limits of quantitation by ddPCR in the matrices within days post dose. In stool, concentrations of onasemnogene abeparvovec DNA were high up to 14 days post dosing. These concentrations declined approximately 4 logs over 30 days post dose, and all patients had levels of onasemnogene abeparvovec in stool below the limit of quantitation (1.1×10^{7} GC/g) by 60 days post dose. Section 6.6 of the SmPC states that caregivers and patient families should be advised on the proper handling of bodily fluids and waste; and instructions should be

	provided regarding good hand-hygiene when coming into direct contact with patient bodily fluids and waste for a minimum of 1 month after treatment. The findings of the shedding study are in line with published data demonstrating that shedding of rAAV vector DNA can be detected for a number of weeks from patient excrements (Favre et al 2001, Manno et al 2006, Provost et al 2005). Shedding is reported to be dependent on the dose and route of administration; the i.v. route can be considered a worst case scenario for AAV shedding. However, even in the case of shedding, the AAV vectors do not propagate outside cells. In summary, shedding of the vector was demonstrated in the completed and ongoing clinical studies. However, as there are no adverse consequences of this spreading reported, the effect is considered insignificant. The likelihood of recombination is very low, due to the characteristics of the vector and proper control for replication competent viruses. In addition, the probability that genetic material would be transmitted from the product is very low due to the fact that there are no mobile elements involved and co-purification of possible genetic impurities (mainly kanamycin resistance gene) is controlled for every batch. The wild type AAV genes have been removed and replaced with DNA needed to produce the SMN protein, leaving behind only the Inverted Terminal Repeats of the AAV genome, which are required to produce SMN and are not sufficient for viral propagation. Additionally, the transgene neither changes the host range or tropism of AAV9, nor does it give any growth/propagation advantage for the vector. Onasemnogene abeparvovec rAAV is incapable of propagating independently. It lacks the genes encoding the wild type AAV replication and capsid proteins. Also, AAV requires a helper virus to replicate. Therefore, propagation of onasemnogene abeparvovec rAAV would require coinfection with both a wild type AAV capable of donating AAV genes and a helper virus (Salganik et al 2015). Such a triple infection is exceedingly unlikely and would be limited in duration by the host immune response. In other words, onasemnogene abeparvovec represents a protein particle containing DNA rather than an infectious agent.
Tumorigenicity due to chromosomal integration	Preclinical data indicate that in most cases, DNA delivered by recombinant AAV vectors predominantly persists as extrachromosomal elements (episomes) rather than integrating into host cell genomes (McCarty et al 2004). Although onasemnogene abeparvovec is not anticipated to integrate into the host cell genome as described above, the long-term consequences of administering AAV viral vectors to humans are not yet fully understood. This is in contrast to wild-type AAV, also non-pathogenic, which has the ability to stably integrate into the host cell genome at a specific site (designated AAVS1) in the human chromosome 19 (Kotin et al 1990, Surosky et al 1997). Since the onasemnogene abeparvovec product uses AAV9 with all of the wild-type DNA removed from the capsids, except for the inverted terminal repeats, the potential risk of incorporation of onasemnogene abeparvovec into the patient chromosomal DNA is thought to be significantly reduced. There are conflicting reports that integration of the wild-type AAV2 genome is associated with induction of hepatocellular carcinoma in a small subset of patients; however there are several studies with evidence to contradict these claims including: a) AAV2 has infected approximately 90% of the human population, b) AAV2 has been shown to possess anticancer activity, c) epidemiological evidence suggests that AAV2 infection plays a protective role against cervical carcinoma, and d) AAV serotypes including recombinant AAV2 and AAV9 have been or are currently used in 162 clinical trials to date in

	which no cancer of any type has been observed or reported (Srivastava, Carter 2017). Further support for the extremely low potential incorporation into host chromosomal DNA comes from pre-clinical studies, which to date have not shown the development of cancer in treated animals including mice and non-human primates exposed to onasemnogene abeparvovec. Long-term effect of onasemnogene abeparvovec therapy is considered Missing Information.
Risk of germline transmission	Onasemnogene abeparvovec utilizes a recombinant AAV9 capsid shell. The non-replicating DNA and capsid does not modify the existing DNA of the patient and hence is not transmitted through the germline. To date, there has been very little evidence of either significant transduction or expression of the SMN transgene in the gonads (ovaries or testes) with onasemnogene abeparvovec in the completed nonclinical studies. Even following systemic i.v. administration, AAV9 vectors (like onasemnogene abeparvovec) appear to distribute to the skeletal muscle, liver, lung and central CNS primarily, with the lowest levels observed in gonad tissues. Importantly, there was no SMN RNA expression in the gonads compared to other tissues (such as those listed above) which exhibited significant levels of expression for up to 24 weeks. Data from other AAV serotypes, including AAV2 (Jakob et al 2005) or AAV2/8 (Ferla et al 2017) showed no adverse effects on male fertility (Jakob et al 2005) or both male and female fertility (Ferla et al 2017), suggesting, that even with some persistence of the AAV vector in these tissues, there were no adverse consequences on fertility or reproduction observed. Although no comparable detailed reproductive assessments have yet been performed with either onasemnogene abeparvovec or other AAV9 vectors, given the tropism of this vector class for other non-gonadal tissues, the likelihood of germline transduction and integration appears minimal. Moreover, even when transducing gonadal cells (spermatagonia) directly, others (Watanabe et al 2017) have suggest that despite the potential for AAV1 to transduce these primary cells in vitro, there was very little risk of germline integration with AAV transduction.
Product quality characteristics and storage and distribution of the product	Onasemnogene abeparvovec is manufactured and released in a GMP environment, using standard techniques and methods well established in the manufacturing of biologics. The product is provided in vials typically used for injectables. The proposed shelf-life for onasemnogene abeparvovec drug product stored at ≤ -60ºC is 2 years. The drug product is shipped frozen.
Adverse events related to administration procedures	There may be pain at the site of the vector infusion as well as bruising surrounding the infusion site. Infections are also possible at the site of the infusion. There were no AEs related to administrative procedures that resulted in irreversible or sustained clinical sequelae.

8.1.2 SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-3 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Hepatotoxicity	TEAEs of elevated transaminases of which some were serious have been observed. In general, these elevations were not associated with clinical symptoms. A case of liver injury was reported in the US Managed Access Program with onasemnogene abeparvovec where the patient was continuing

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	treatment with nusinersen and had AST and ALT elevations of > 3 x ULN before treatment with onasemnogene abeparvovec. The patient recovered with additional steroid therapy. The benefit of onasemnogene abeparvovec as an effective treatment for the debilitating and life-threatening condition SMA outweighs the important identified risk 'hepatotoxicity' that could be serious and potentially life-threatening if not treated. Elevated transaminases can be minimised in clinical practice through monitoring of liver enzymes and prednisolone treatment.
Transient thrombocytopenia	A transient decrease in platelet counts has been observed, typically at Day 7. Decreases were clinically asymptomatic, transient and resolved during the observation period. The benefit of onasemnogene abeparvovec as an effective treatment for the debilitating and life-threatening condition SMA outweighs the important identified risk of transient thrombocytopenia that could be serious if not treated. Platelet counts will be monitored post-treatment during the first month.

Table 8-4 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Cardiac adverse events	Cardiac degeneration, fibrosis and atrial thrombosis were reported in non-clinical toxicity studies in mice. The underlying mechanism of these findings is not known. The available clinical cardiovascular safety data do not provide sufficient evidence to confirm a causal association with onasemnogene abeparvovec. Cases of tachycardia and bradycardia occurred; however, the significance was not determined. Minor transient increases in CK- MB and troponin I were reported with no associated clinical sequelae. The benefit of onasemnogene abeparvovec as an effective treatment for the debilitating and life-threatening condition SMA outweighs the important potential risk of cardiac AEs that has yet to be confirmed.
Use in patients with ant-AAV9 antibody titres > 1:50 and higher vector loads required	Patients with AAV9 titres > 1:50 were excluded from clinical studies thus, the safety of onasemnogene abeparvovec in this population is unknown. Increases in anti-AAV9 titres were observed after the administration of onasemnogene abeparvovec during clinical studies. This response was expected however, there were no apparent relationships between anti-AAV9 titre and safety or efficacy.
Dorsal root ganglia cell inflammation	A non-clinical study entitled "Non-GLP Histopathology Evaluation of the Safety of Intrathecal Delivery of AVXS-101 Alone or in Combination with Contrast Agents (A or B) in Cynomolgus Macaques (*Macaca fascicularis*) (ITFS-101)" was performed in non-human primates and concluded that most animals receiving i.t. injection of onasemnogene abeparvovec developed minimal to marked DRG mononuclear cell inflammation at some or all examined levels (cervical to sacral). Inflammation was present at similar incidence and severity in animals given onasemnogene abeparvovec alone or in combination with either Contrast Agent A or Contrast Agent B. The non-clinical findings of DRG inflammation have not been confirmed in patients from both clinical trials as well as post-marketing experience.

Table 8-5 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term efficacy of onasemnogene abeparvovec therapy	The long-term efficacy and safety of onasemnogene abeparvovec therapy in light of adverse events that are rare or have long latency, cannot be defined based on available evidence. As of 31-Dec-2019, 13 of the 15 subjects (86.7%) who completed Study CL 101 were enrolled in the long-term follow-up study (Study LT-001). Patients in Study LT-001 have been followed for up to 68.6 months with observation ongoing. The long-term effect of onasemnogene abeparvovec therapy is considered missing information and will be monitored to ensure that the risk-benefit balance of the product is maintained.
Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required	There is the potential for risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required. The principal safety concerns for the higher number of SMN2 copies relates to the prevalence of anti-AAV9 antibodies at the initiation of therapy with onasemnogene abeparvovec and the higher viral loads required due to increased body weight. No apparent relationship has been found between anti-AAV9 antibody titre and efficacy or safety of onasemnogene abeparvovec. The product is ordered from the manufacturer on an individual per patient basis. Therefore, the chances for off-label usage are extremely small. Nevertheless, as a missing information, information related to off label use will be collected and characterized, if applicable, in Study AVXS-101-RG-001.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The following risk previously classified as not important in RMP Version 2.2 was reclassified in RMP Version 3.0 based on increasing evidence from the literature and emerging from other gene therapies clinical development that DNA integration events can occur with rAAV therapy: the potential risk of Tumorigenicity Due to Chromosomal Integration.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Hepatotoxicity

Table 8-6 Clinical trial data of Hepatotoxicity

Preferred term	Study CL-101			Study CL-303	Study CL-304	Study CL-302	Therapeutic i.v. dose (N=97) n (%)
	Low dose (N=3) n (%)	Proposed therapeutic dose (N=12) n (%)	All (N=15) n (%)	1.1 E14 vg/kg (N=22) n (%)	1.1 E14 vg/kg (N=30) n (%)	1.1 E14 vg/kg (N=33) n (%)	
Alanine aminotransferase increased	0	0	0	5 (22.7)	4 (13.3)	9 (27.3)	18 (18.6)
Aspartate aminotransferase increase	0	1 (8.3)	1 (6.7)	6 (27.3)	7 (23.3)	8 (24.2)	22 (22.7)
Gamma-glutamyl transferase increased	0	0	0	2 (9.1)	2 (6.7)	1 (3.0)	5 (5.2)
Transaminases increased	1 (33.3)	3 (25.0)	4 (26.7)	2 (9.1)	0	0	5 (5.2)
Liver function test increased	0	0	0	0	1 (3.3)	0	1 (1.0)
Hypertransaminasaemia	0	0	0	0	0	8 (24.2)	8 (8.2)
Hepatic steatosis	0	0	0	0	0	1 (3.0)	1 (1.0)

Data cut-off date: 12-Nov-2020
Source: Integrated Summary of Safety
MedDRA version 21.0

Table 8-7 Important identified risk: Hepatotoxicity: Other details

Hepatotoxicity	Details
Potential mechanisms	The administration of an AAV vector has the risk of causing elevated transaminases and immune-mediated hepatotoxicity. A certain capsid load may activate capsid-specific T cells that may lead to hepatotoxicity and loss of transgene expression (Kuranda and Mingozzi 2017).
Evidence source(s) and strength of evidence	**Clinical trials**: Transaminase elevations have been observed without association with clinical signs or symptoms. **Early access programs and post-marketing reports**: Adverse events of transaminase elevations are commonly reported following onasemnogene abeparvovec administration. In the post-marketing setting, several cases of ALF have been reported, some of which had fatal outcomes.
Characterization of the risk	Hepatic adverse events are commonly reported in clinical trials, early access programs and post-marketing surveillance. These events are generally transaminase elevations without association with clinical

Hepatotoxicity	Details
	symptoms. The incidence of hepatic adverse events in clinical trials as of 12-Nov-2020 is summarized in Table 8-6. No case of isolated liver failure was reported in clinical trials. In early access programs, registry and post-marketing surveillance, several cases of acute liver failure or liver failure were reported. Two fatal cases were reported in the post-marketing setting; in both cases, clinical presentations of hepatotoxicity started 1-10 days following the initiation of prednisolone taper, and patients died 6-7 weeks after onasemnogene abeparvovec dosing.
Risk factors and risk groups	Patients with impaired liver function Data from a small study in children weighing ≥8.5 kg to ≤21 kg (aged approximately 1.5 to 9 years), indicate a higher frequency of aspartate aminotransferase (AST) or alanine transaminase (ALT) elevations (in 23 out of 24 patients) compared with frequencies of AST/ALT elevations observed in other studies in patients weighing <8.5 kg (in 31 out of 99 patients).
Preventability	In order to mitigate potential for hepatotoxicity, patients should have liver function tests (ALT, AST, total bilirubin, albumin, prothrombin time, partial thromboplastin time [PTT], and international normalized ratio [INR]) conducted at baseline, and ALT, AST, total bilirubin should be monitored at regular intervals for at least 3 months following onasemnogene abeparvovec infusion (weekly in the first month and during the entire corticosteroid taper period, followed by every two weeks for another month), and at other times as clinically indicated. Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly clinically assessed and monitored closely. In case hepatic injury is suspected, prompt consultation with a paediatric gastroenterologist or hepatologist, adjustment of the recommended immunomodulatory regimen and further testing is recommended (e.g. albumin, prothrombin time, PTT, and INR). Patients with ALT, AST, total bilirubin levels (except due to neonatal jaundice) > 2 × ULN, or positive serology for hepatitis B or C have not been studied in clinical studies with onasemnogene abeparvovec. Onasemnogene abeparvovec therapy should be carefully considered in patients with hepatic impairment (SmPC). Patients should be treated with prednisolone before and after onasemnogene abeparvovec infusion. Pretreatment with oral prednisolone should be given 24 hours prior to infusion with onasemnogene abeparvovec at a dose of 1 mg/kg/day. If at any time patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a pediatric gastroenterologist or hepatologist and adjustment to the recommended immunomodulatory regimen, including increased dose, longer duration or prolongation of corticosteroid taper, should be considered. If oral corticosteroid therapy is not tolerated intravenous corticosteroid therapy may be considered as clinically indicated. Tapering of prednisolone should not be considered until AST/ALT levels are less than 2 × ULN and all other assessments (e.g. total bilirubin) return to normal range (SmPC). If the patient is clinically stable with unremarkable findings at the end of the corticosteroid taper period, liver function should continue to be monitored every two weeks for another month.

Hepatotoxicity	Details
Impact on the benefit-risk balance of the product	Hepatotoxicity may have a significant impact on patients requiring hospitalization or may be life-threatening in serious cases. However, as hepatotoxicity can be minimized in clinical practice through use of prednisolone and monitoring of liver function tests, it is not expected to change the favorable benefit-risk of onasemnogene abeparvovec that is used to treat a debilitating and life-threatening condition. Additional pharmacovigilance activities will further characterize the risk with respect to number of reports, seriousness, outcome, and risk factors (Part III).
Public health impact	Minimal due to the rarity of the condition

8.3.1.2 Important identified risk: Transient thrombocytopenia

Table 8-8 Clinical trial data of Transient thrombocytopenia

SMQ Preferred Term	Study CL-101 Low Dose (N=3) n (%)	Study CL-101 Proposed Therapeutic Dose (N=12) n (%)	Study CL-101 All (N=15) n (%)	Study CL-303 1.1 E14 vg/kg (N=22) n (%)	Study CL-304 1.1 E14 vg/kg (N=30) n (%)	Study CL-302 1.1 E14 vg/kg (N=33) n (%)	Therapeutic i.v. dose (N=97) n (%)
Platelet count decreased	0	0	0	1 (4.5)	1 (3.3)	0	2 (2.1)
Thrombocytopenia	0	0	0	2 (9.1)	1 (3.3)	1 (3.0)	4 (4.1)

Data cut-off date: 12-Nov-2020
Source: Integrated Summary of Safety
MedDRA version 21.0

Table 8-9 Important identified risk: Transient thrombocytopenia: Other details

Transient thrombocytopenia	Details
Potential mechanisms	The exact mechanism is not known.
Evidence source(s) and strength of evidence	**Clinical trials**: Transient thrombocytopenia was observed in onasemnogene abeparvovec clinical studies. In most cases, the lowest platelet value occurred the first week following onasemnogene abeparvovec infusion. **Early access programs and post-marketing reports**: Adverse events of thrombocytopenia or decreased platelet counts are commonly reported after onasemnogene abeparvovec administration. These events are generally not clinically significant. Post-marketing cases with platelet counts < 50 × 10^9/L and <25 x 10^9/L have been reported to occur within three weeks following onasemnogene abeparvovec administration.
Characterization of the risk	Thrombocytopenia or decreased platelet counts were commonly reported in clinical trials, early access programs and post-marketing surveillance. These events were generally not associated with clinical significance (e.g., bleeding events). The incidence of thrombocytopenia events in clinical trials are summarized in Table 8-8.

Transient thrombocytopenia	Details
Risk factors and risk groups	Data from a small study in children weighing ≥8.5 kg to ≤21 kg (aged approximately 1.5 to 9 years), indicate a higher frequency of thrombocytopenia (in 20 out of 24 patients) compared with frequencies of thrombocytopenia observed in other studies in patients weighing <8.5 kg (in 22 out of 99 patients).
Preventability	Platelet counts should be obtained before onasemnogene abeparvovec infusion and should be closely monitored within the first three weeks following infusion and on a regular basis afterwards, at least weekly for the first month and every other week for the second and third months until platelet counts return to baseline.
Impact on the benefit-risk balance of the product	Thrombocytopenia may have a significant impact on the patient should it occur. However, it is not expected to impact the risk-benefit balance of onasemnogene abeparvovec that is used to treat a debilitating and life-threatening condition. Additional pharmacovigilance activities will further characterize the risk with respect to number of reports, seriousness, outcome, and risk factors (Part III).
Public health impact	Minimal due to the rarity of the condition

8.3.1.3 Important identified risk: Thrombotic microangiopathy

Table 8-10 Important identified risk: Thrombotic microangiopathy

Thrombotic microangiopathy	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Cases of TMA were reported in 23 patients in the post-marketing setting, early access programs, and the registry, cumulatively up to post-marketing DLP 23-May-2022. Of these, in 12 patients, diagnosis of TMA was supported by available clinical details. All 12 confirmed TMA cases were reported within 1-2 weeks post onasemnogene abeparvovec infusion. TMA is characterized by acute and/or chronic uncontrolled dysregulation and/or excessive activation of the alternative pathway of complement, and its etiology can be genetic or acquired, occurring in both children and adults (Kaplan et al 2014). TMA is a life-threatening condition (Joly et al 2018), with fatal outcomes reported. In 2020, the incidence of TMA in children is estimated to be three cases/million/year (Joly et al 2018). Although the incidence of TMA in children with SMA is unknown, recent literature suggests coagulation abnormalities can occur inherently in this population (Wijngaarde et al 2020). A genetic predisposition to TMA has been associated with mutations in the genes encoding complement factor H, complement factor I, complement factor B, membrane cofactor protein, C3, and thrombomodulin, as well as autoantibodies against complement factor H or complement factor I have been reported. In rare conditions, atypical hemolytic uremic syndrome is due to mutation in diacyglycerol kinase ε or deficiency of cobalamin C. Acquired TMA can occur in association with a wide range of viral, bacterial, fungal, and parasitic infections, although it is frequently unclear if this is a

Thrombotic microangiopathy	Details
	direct effect of the pathogen, an adverse reaction to the treatment of an infection, or a trigger that unmasks a latent complement defect. Furthermore, encapsulated organisms have been identified as a trigger; capsular polysaccharide is a critical virulence factor that enables immune evasion. Although an exact mechanism for TMA is unknown, given its rarity in the general population, the number of cases reported for the patients with the rare disease (SMA), and similar pattern of time to onset of TMA, a causal association between onasemnogene abeparvovec and TMA is plausible.
Characterization of the risk	In 12 patients, diagnosis of TMA was supported by available clinical details. • All these cases occurred between 1-2 weeks after onasemnogene abeparvovec administration. • All these cases had a classic clinical triad of thrombocytopenia, hemolytic anemia, and acute renal injury. • The reported clinical presentations were consistent with a life-threatening condition, as indicated by the CTCAE grade 4 decrease in platelet counts (< 25,000) in 11 confirmed cases. • Invasive interventions (plasmapheresis, dialysis, hemofiltration or/and transfusions) were performed in 8 cases. • In 7 cases, the patients had previous exposure to nusinersen. • Concurrent bacterial infection was reported in 5 cases. One of the patients with concurrent infection also presented clinical signs and laboratory evidence for dehydration and anemia at baseline. • The majority of these cases were reported for female patients. • Recovery from TMA was reported in 8 cases. In other 2 cases, laboratory test results indicated normalized or progressively improving platelet count, renal function tests, and hemoglobin values. Outcome was not assessable in one case due to lack of sufficient clinical details. Fatal outcome was reported in 1 patient, who died due to a complicated clinical course leading to fatal septic shock (described in detail below). • Fatal outcome due to sepsis was reported in one patient after resolution of TMA. In addition, 1 fatal case occurred with reported diagnosis of TMA. However, TMA could not be confirmed with certainty based on the reported information, which was more consistent with shock. The benefit of onasemnogene abeparvovec as an effective treatment for the debilitating and life-threatening condition SMA outweighs the important identified risk of TMA that in serious in nature but is clinically recognizable and effectively treatable.
Risk factors and risk groups	Infections and vaccinations
Preventability	Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes. Thrombocytopenia is a key

Thrombotic microangiopathy	Details
	feature of TMA, therefore platelet counts should be closely monitored within the first three weeks following infusion and on a regular basis afterwards. In case of thrombocytopenia, further evaluation including diagnostic testing for hemolytic anemia and renal dysfunction should be promptly undertaken. If patients show clinical signs, symptoms or laboratory findings consistent with TMA, a specialist should be consulted immediately to manage TMA as clinically indicated. Caregivers should be informed about signs and symptoms of TMA and should be advised to seek urgent medical care if such symptoms occur.
Impact on the benefit-risk balance of the product	Given the significant progressive debilitating nature of SMA and that TMA can be managed with timely detection and medical intervention, the risk-benefit balance of onasemnogene abeparvovec remains favorable.
Public health impact	Minimal due to the rarity of the condition

8.3.1.4 Important potential risk: Cardiac adverse events

Table 8-11 Important potential risk: Cardiac adverse events

Cardiac adverse events	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Non-clinical**: Cardiac degeneration, fibrosis and atrial thrombosis were reported in non-clinical toxicity GLP studies in mice (doses in mice were higher compared to human doses). **Clinical**: Cardiac-related non-clinical findings have not been observed in humans. Minor transient increases in CK-MB and troponin I were reported with no associated clinical sequelae. Cases of tachycardia and bradycardia also occurred. However, the significance of elevated cardiac enzymes or changes in heart rates cannot be determined given the available data.
Characterization of the risk	**Study CL-101** Five (5) patients PD had a patent foramen ovale detected on echocardiography. This is a common congenital abnormality which is present in 10% to 35% of the general population, and because this was present at the screening echocardiogram for each patient prior to onasemnogene abeparvovec administration, it is reasonable to conclude that this finding was unrelated to administration of onasemnogene abeparvovec. Of these patients, 1 patient PD had an additional echocardiogram finding of "trivial aortic root and sinotubular junction dilation" reported at visit 17, which was assessed as not clinically significant. The other 4 patients had no other abnormalities reported. **Cardiac markers** **Study CL-101** All patients enrolled in Study CL-101 had elevated CK-MB levels at baseline and at the majority of assessments during the study; however, none of the elevations in CK-MB were considered clinically significant by

Cardiac adverse events	Details
	the study investigator. The mean (SD) change from baseline in CK-MB at the final assessment (Month 24) among all patients (n = 11) was a decrease of 3.26 (8.04) µg/L (range -19.9 to 4.7 µg/L). All observed elevations in CK-MB were clinically asymptomatic. Eight (8) of 15 patients (53.3%) had elevations in cardiac troponin I levels that met the pre-specified potentially clinically significant protocol criterion (> 0.5 µg/mL). Of these 8 patients, 2 (25.0%) had elevated cardiac troponin I levels prior to administration of onasemnogene abeparvovec. The mean (SD) change from baseline in cardiac troponin I at Month 24 among all patients with values (n = 11) was a decrease of 0.0065 (0.014) µg/mL (range -0.048 to 0.000 µg/mL). None of the elevations in cardiac troponin I observed during the study were considered clinically significant by the investigator. By the end of the study all values had either returned to within the normal range or no longer met the pre-defined criterion for clinical significance. **Study AVXS-101-LT-001** Measurements of CK-MB and troponin I, ECG, Holter monitoring or echocardiogram were not included in the study. **Study AVXS 101 CL 303** The baseline mean (± standard deviation) CK-MB value was 12 µg/L (±7). Mean change from baseline in post-treatment CK-MB values ranged from –0.2 µg/L at Day 14 to +10.4 µg/L at Month 9. Individual subject change indicates no trends of changes in CKMB values over time. The majority of patients in each study have high baseline values and show no shift from baseline to maximum or final values. **Study AVXS-101-CL-304** Two of 14 (14.3%) patients with 2 copies of SMN2 had a total of 3 AESIs related to cardiotoxicity, including 1 patient (7.1%) with blood creatine phosphokinase increased and 1 patient (7.1%) with 2 AESIs of troponin increased. Two of 15 (13.3%) patients with 3 copies of SMN2 had a total of 3 AESIs related to cardiotoxicity, including 2 patients (13.3%) with troponin increased, and 1 patient (6.7%) with blood creatine phosphokinase MB increased. All AESIs related to troponin elevation were considered possibly, probably, or definitely related to treatment by the investigator. All AESIs related to troponin recovered or resolved, and none of them required treatment. All AESIs related to creatine phosphokinase were considered either possibly or probably related to treatment by the investigator. All AESIs related to creatine phosphokinase recovered or resolved, and neither of them required treatment. All of the AESIs related to troponin and creatine phosphokinase were mild in severity (CTCAE Grade 1). In the 2 copy SMN2 cohort patients, troponin I ranged from as low as 0.0 µg/L to as high as 0.2 µg/L at the Day 30 visit. In the 3 copy SMN2 cohort troponin ranged from as low as 0.0 to as high as 0.2 µg/L at the Day 7 visit. In all patients in Study CL-304, ECG changes were consistent with normal development. None of the ECG changes were reported as TEAEs.

Cardiac adverse events	Details
	There were no TEAEs related to echocardiogram findings. **Study AVXS-101-CL-302** Mean (± standard deviation) CK-MB at baseline was 22.7 µg/L (±11.6). Mean change from baseline in post-treatment CK-MB values ranged from –8.4 µg/L (±10.6) at Month 15 to 1.7 µg/L at Month 8 (single observation). Overall, Mean CK-MB ranged from 14.9 µg/L (±7.2) at Month 1 to a maximum of 23.5 µg/L (±10.1) at Month 6, with exception of Month 8, which had only one observation (7.4 µg/L). Mean (± standard deviation) troponin I at baseline was 0.02 µg/L (±0.0, n=3). Mean change from baseline in post-treatment troponin I values ranged from 0.0 µg/L (±0.0, n=4) at Month 6 to 0.027 µg/L (±0.023, n=3) at Month 1. The maximum mean troponin I value was 0.047 µg/L (±0.023, n=3) and occurred at the Month 1. Bradycardia and tachycardia were reported for one patient both of which were not considered to be related to AVXS 101. Except for one patient, all CK-MB values were above the ULN at baseline. For 16 of the 21 (76.2%) patients with post-treatment CK-MB results, the last recorded CK-MB value was below that recorded at baseline. One patient experienced an increase from baseline in QTcF of ≥30 msec. No consistent trends in the changes from baseline in the ECG parameters were observed. Two patients with echocardiogram results post baseline did not show any significant changes. No TEAEs for the cardiac markers, ECG or echocardiogram findings were reported at the time of the data cut off.
Risk factors and risk groups	Underlying cardiac abnormalities
Preventability	Troponin I should be obtained at baseline and monitored for at least 3 months following onasemnogene abeparvovec infusion or until levels return to within normal reference range for SMA patients. Consultation with pediatric cardiologist is recommended to determine clinical significance of elevated troponin I.
Impact on the benefit-risk balance of the product	Cardiac AEs may have a significant impact on the patient should they occur. However, it is not expected to impact the risk-benefit of onasemnogene abeparvovec that is used to treat a debilitating and life-threatening condition. Additional pharmacovigilance activities will further characterize the risk with respect to number of reports, seriousness, outcome, and risk factors (Part III).
Public health impact	Minimal due to the rarity of the condition

8.3.1.5 Important potential risk: Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required

Table 8-12 Important potential risk: Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required

Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Clinical:** Patients with AAV9 titres > 1:50 have not been studied in onasemnogene abeparvovec clinical studies. After administration of onasemnogene abeparvovec, increases in anti-AAV9 titres were observed. This is considered an expected response, and there were no apparent relationships between anti-AAV9 titre and safety or efficacy. It is not known whether administration of the onasemnogene abeparvovec vector represents a risk for patients with anti-AAV9 antibodies at higher titres.
Characterization of the risk	Administration of AAV9 vector may result in a potential immune response risk for patients with high levels of pre-existing antibodies against the AAV9 capsid. **Study AVXS-101-CL-101** In Study CL-101, all treated patients had anti AAV9 titres ≤ 1:50 at baseline. As expected, increases in anti-AAV9 titre were observed in all patients, reflecting normal antibody response to foreign (viral) antigen. **Study AVXS-101-CL-303** Patients had subsequent increases in anti-AAV9 titres after administration of onasemnogene abeparvovec. **Study AVXS-101-CL-304** Anti-AAV9 titres were assessed in biological mothers of patients at screening. Of the mothers, one had a titre of 1:50 at screening. All other titres were negative. Patient antibodies were to be evaluated when the maternal antibody titre is > 1:50. **Study AVXS-101-CL-302** All patients had anti-AAV9 titres ≤ 1:50 prior to administration of onasemnogene abeparvovec. As of the DLP (12-Nov-2020), there is no evidence to suggest an impact of post-dose antibodies on safety endpoints.
Risk factors and risk groups	Patients with anti-AAV9 titres > 1:50 prior to administration of onasemnogene abeparvovec.
Preventability	Patients should be tested for the presence of anti-AAV9 antibodies prior to infusion with onasemnogene abeparvovec.

Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required	Details
Impact on the benefit-risk balance of the product	It is not expected to impact the risk-benefit of onasemnogene abeparvovec that is used to treat a debilitating and life-threatening condition. Additional pharmacovigilance activities will further characterize the risk as onasemnogene abeparvovec is also being investigated in other types of SMA including patients who may be older.
Public health impact	Minimal due to the rarity of the condition

8.3.1.6 Important potential risk: Dorsal root ganglia toxicity

Table 8-13 Important potential risk: Dorsal root ganglia toxicity

Dorsal root ganglia toxicity	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Clinical**: No adverse events suggestive of ganglionopathy were observed in patients treated with onasemnogene abeparvovec from clinical trials, early access programs, registry and post-marketing clinical experience in whom treatment with steroids was administered. All available autopsy reports of fatal cases in the post-marketing setting are being monitored for evidence of DRG toxicity. A limited number of autopsy reports received for the post-marketing cases until 23-May-2022 did not indicate histological evidence of DRG toxicity. **Non-clinical**: In cynomolgus monkeys, i.t. and i.v. administration of onasemnogene abeparvovec has been associated with clinically silent (asymptomatic) microscopic changes in the DRG and/or trigeminal ganglia. The findings in the DRG (at all levels) and/or trigeminal ganglia included mononuclear cell inflammation, neuronal degeneration, satellitosis, and/or neuronal necrosis. These non-clinical DRG findings have not been confirmed in patients from both clinical trials as well as post-marketing experience. Based on data accumulated so far from the GLP non-human primate studies at terminal intervals up to 6 weeks post dose, the OAV101-related DRG finding is reclassified from “DRG cell inflammation” to “DRG toxicity” given that the microscopic findings are generally characterized by mononuclear cell inflammation, neuronal degeneration, satellitosis, neuronal loss, gliosis and/or axonal degeneration. In addition, secondary changes in the spinal cord and peripheral nerves of axon degeneration have been observed.
Characterization of the risk	Unknown
Risk factors and risk groups	Unknown
Preventability	Unknown

Dorsal root ganglia toxicity	Details
Impact on the benefit-risk balance of the product	It is not expected to impact the risk-benefit of onasemnogene abeparvovec that is used to treat a debilitating and life-threatening condition.
Public health impact	Minimal due to the rarity of the condition

8.3.1.7 Important potential risk: Tumorigenicity due to chromosomal integration

Table 8-14 Important potential risk: Tumorigenicity due to chromosomal integration

Risk of tumorigenicity due to chromosomal integration	Details
Potential mechanisms	Onasemnogene abeparvovec is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Rare instances of random vector integration into human DNA are possible with recombinant AAV.
Evidence source(s) and strength of evidence	There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity.
Characterization of the risk	Integration of wild-type AAV genomes has been found in humans. AAV is prevalent in the environment, leading to natural AAV infection. The wild-type AAV genome can integrate into a genomic locus known as AAVS1 in human cells to establish latency. This phenomenon is in part due to the sequence similarity found within AAVS1, and the inverted terminal repeats (ITR) and activity of the Rep gene contained within the wild-type AAV genome (Wang et al 2019, Monahan et al 2021, Sabatino et al 2022). Recombinant AAV vectors do not contain any viral genes, do not encode the AAV Rep protein, and therefore integrate with a much lower efficiency and without specificity for AAVS1 into the host DNA compared to wild-type AAV (Monahan et al 2021). Studies in cell lines and in mouse models have observed near-random integration that favored actively transcribed regions of the genome. A study that utilized a partial hepatectomy mouse model to evaluate the relative proportion of extrachromosomal vs chromosomally integrated forms of vector genome estimated that <10% of the AAV genomes were integrated (Nakai et al 2001, Sabatino et al 2022). While the likelihood of insertional mutagenesis by AAV vectors is considered to be low, studies showing integration of rAAV vectors into the host genome in animal models raise a potential safety concern in terms of the risk of insertional mutagenesis and carcinogenesis occurring in humans. There are limited data available on rAAV vector genome integration in humans. Analysis by (Kaeppel et al 2013) of human muscle biopsies after the delivery of an rAAV1 encoding for the LPLS447X gene revealed that vector genomes were heterogeneously distributed throughout the tissue with detectable levels of vector integration. Integration sites were distributed across the host genome with main integration hotspots within

Risk of tumorigenicity due to chromosomal integration	Details
	mitochondrial genes and nuclear mitochondrial DNA regions. (Gil-Farina et al 2016) characterized the integration of both complete and partial rAAV2/5 genomes in liver biopsies from a clinical trial aimed to treat acute intermittent porphyria. The study confirmed that AAV integration was both low in frequency and distributed genome-wide, with no clustered integration sites near genes that had been previously implicated in the mouse studies. Nonetheless, the number of integration sites retrieved in those samples was small, most likely because patients received a sub-therapeutic dose and little material was used as input, thus hampering the ability to draw conclusions and establish a comparison with preclinical datasets (Sabatino et al 2022). Based on limited available data so far, it appears that the risk of insertional mutagenesis and tumorigenesis with rAAV-vector-based therapies is very low, but cannot be excluded. Two recently approved gene therapies that use an AAV5-based vector, etranacogene dezaparvovec-drlb (Hemgenix) and valoctocogene roxaparvovec (Roctavian), collected information on integration into the host genome in their respective clinical development studies. **Study AVXS-101-LT-001** In Study LT-001, in the event a patient undergoes a tissue biopsy for a tumor or for any reason, an additional tissue biopsy sample may be requested for further analysis. These additionally obtained tissue samples will be used for conducting further analyses that may include but not limited to genomic integration analysis and molecular localization. **Study AVXS-101-LT-002** In Study LT-002, in the event a patient undergoes a tissue biopsy for a tumor or for any reason, an additional tissue biopsy sample may be requested for further analysis. These additionally obtained tissue samples will be used for conducting further analyses that may include but not limited to genomic integration analysis and molecular localization.
Risk factors and risk groups	Unknown
Preventability	Unknown
Impact on the benefit-risk balance of the product	Unknown
Public health impact	Minimal due to the rarity of the condition

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-15 Missing information: Long-term efficacy of onasemnogene abeparvovec therapy

Long-term efficacy of onasemnogene abeparvovec therapy	Details
Evidence source	All 15 patients (100%) treated with onasemnogene abeparvovec have completed the 24-month study period in AVXS-101-CL-101 and 13 of them were enrolled in Study AVXS-101-LT-001 as of DLP.
Population in need of further characterization	The long-term risks cannot be defined based on the available data and thus the safety profile will be derived from routine and additional pharmacovigilance activities. Patients that completed Study AVXS-101-CL-101 will be followed for 15 years as part of a separate long-term follow-up study (AVXS-101-LT-001). Likewise, Study LT-002 will follow patients for 15 years in those patients who have completed Studies AVXS-101-CL-303, AVXS-101-CL-304, AVXS-101-CL-302 respectively. In addition, a long-term registry (AVXS-101-RG-001, or RESTORE) will follow patients for 15 years.

Table 8-16 Missing information: Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required	Details
Evidence source	None
Population in need of further characterization	The risk/benefit balance in other types of SMA and/or other administration routes is not known. Study AVXS-101-CL-304 will evaluate the safety of onasemnogene abeparvovec in patients with SMA types 2 and 3.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events • Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required • Dorsal root ganglia toxicity • Tumorigenicity due to chromosomal integration
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy • Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists (Annex 4) will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- **Hepatotoxicity**
  Elevated liver enzymes checklist
- **Transient thrombocytopenia**
  Decreased platelets checklist
- **Thrombotic microangiopathy**
  TMA checklist
- **Cardiac adverse events**
  Cardiac adverse event checklist
- **Dorsal root ganglia toxicity**
  Sensory neuronopathies checklist

Other forms of routine pharmacovigilance activities for risks

None.

10.2 Part III.2. Additional pharmacovigilance activities

AVXS-101-LT-001:

A long-term follow-up safety study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering onasemnogene abeparvovec.

Rationale and study objectives:

To collect long-term follow-up safety data of patients with SMA Type 1 who were treated with onasemnogene abeparvovec in the AVXS-101-CL-101 study.

Study design:

Fifteen-year safety follow-up study of patients rolling over from AVXS-101- CL-101, consisting of an initial 5-year phase (annual visits) with a subsequent 10-year observational phase (phone contact at least annually).

Study population:

SMA Type 1

Milestones:

- Study report: Q4 2033

AVXS-101-LT-002: A long term follow up study of patients in the clinical trials for SMA Type 1 Delivering onasemnogene abeparvovec

Rationale and study objectives:

To collect long term, follow up safety and efficacy data in patients with SMA who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial.

Study design:

Interventional

Study population:

Patients diagnosed with SMA Types 1, 2 or 3 (with 2, 3, or 4 copies of SMN2)

Milestones:

- Study Report: Q3 2036

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study AVXS-101-LT-001 Ongoing	To collect long-term follow-up safety data of patients with SMA Type 1 who were treated with onasemnogene abeparvovec in the AVXS-101-CL-101 study	• Hepatotoxicity • Thrombotic microangiopathy • Transient thrombocytopenia • Cardiac adverse events • Dorsal root ganglia toxicity • Tumorigenicity due to chromosomal integration • Long-term efficacy of onasemnogene abeparvovec therapy	Final study report	Q4 2033
Study AVXS-101-LT-002 Ongoing	To collect long-term follow-up safety and efficacy data in patients with SMA Type 1, Type 2 or Type 3 who were treated with onasemnogene abeparvovec in a clinical trial.	• Hepatotoxicity • Thrombotic microangiopathy • Transient thrombocytopenia • Cardiac adverse events • Dorsal root ganglia toxicity • Tumorigenicity due to chromosomal integration • Long-term efficacy of onasemnogene abeparvovec therapy	Final study report	Q3 2036

11 Part IV: Plans for post-authorization efficacy studies

Table 11-1 Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Study AVXS-101-RG-001 Ongoing	To assess the effectiveness of treatments for SMA, the overall survival of patients with SMA and the patient's functional independence.	Long-term efficacy	Final study report	2038

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Hepatotoxicity	**Routine risk communication:** SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3 PL Sections 2, 3, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for monitoring of liver function tests prior to treatment and treatment with prednisolone in SmPC Sections 4.2, 4.4; PL Section 3 • Recommendations for routine monitoring of liver function tests in SmPC Section 4.4; PL Section 2 **Other routine risk minimization measures beyond the Product Information:** None
Transient thrombocytopenia	**Routine risk communication:** SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring of platelet counts in SmPC Section 4.4 How to detect signs of low platelet counts in the PL Section 2 **Other routine risk minimization measures beyond the Product Information:** None
Thrombotic microangiopathy	**Routine risk communication:** SmPC Sections 4.2, 4.4, 4.8 PL Sections 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Requirement for Baseline laboratory testing of creatinine and complete blood count is mentioned in SmPC Section 4.2. Section 4.4 of the SmPC provides recommendation on close monitoring of platelet counts, and on testing for hemolytic anemia and renal dysfunction. It also recommends the need for urgent medical care if the physician and caregivers observe signs and symptoms of TMA. **Other routine risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
	None
Cardiac adverse events	**Routine risk communication:** SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3 PL Sections 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for monitoring troponin I levels in SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** None
Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required	**Routine risk communication:** SmPC Sections 4.2, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec (SmPC Section 4.4) **Other routine risk minimization measures beyond the Product Information:** None
Dorsal root ganglia toxicity	**Routine risk communication:** SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Tumorigenicity due to chromosomal integration	**Routine risk communication:** SmPC Sections 4.4, 5.1 PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Long-term efficacy of onasemnogene	**Routine risk communication:** None

Safety concern	Routine risk minimization activities
abeparvovec therapy	**Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

12.2 Part V.2. Additional Risk minimization measures

Educational material

Healthcare professional guide

Objectives:

To mitigate possible risks before the start of treatment, at the time of the infusion, and after infusion by providing healthcare professionals with a guide on the following safety areas of concern:

- Hepatotoxicity
- Thrombotic microangiopathy

Rationale for the additional risk minimization activity:

To create a guide to help prescribers prepare a local checklist or summary materials to help to mitigate risks.

Target audience:

Healthcare professionals who are expected to prescribe, dispense and administer Zolgensma.

Plans to evaluate effectiveness of the risk minimisation measures and criteria for success.

The effectiveness of risk mitigation of hepatotoxicity, and thrombotic microangiopathy will be assessed in the context of risk evaluation in the PSUR.

Educational material

Caregiver information guide

Objectives:

To mitigate possible risks post-infusion by providing patients/caregivers with an educational guide on the following safety areas of concern:

- Hepatotoxicity
- Thrombotic microangiopathy
- Thrombocytopenia (low platelet count)
- Other important aspects related with patient management (e.g. need for concomitant treatment with corticosteroids; monitoring vomiting to ensure corticosteroid uptake; signs and symptoms of infection; importance of observing overall health status including hydration, nutrition, and prevention of infections).

Rationale for the additional risk minimization activity:

To increase understanding of caregivers on the known risks which can be mitigated with actions before and following onasemnogene abeparvovec one-time administration, and with prompt contact of healthcare services.

Target audience:

Caregivers of patients in whom onasemnogene abeparvovec treatment is planned or who have received onasemnogene abeparvovec.

Plans to evaluate effectiveness of the risk minimisation measures and criteria for success.

The effectiveness of risk mitigation of hepatotoxicity, thrombotic microangiopathy, and thrombocytopenia/low platelet count will be assessed in the context of risk evaluation in the PSUR.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8. 5.2, 5.3 PL Sections 2, 3, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow up questionnaire
	Additional risk minimization measures: Healthcare professional guide Caregiver information guide	**Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Transient thrombocytopenia	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow up questionnaire
	Additional risk minimization measures: Caregiver information guide	**Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Thrombotic microangiopathy	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8 PL Sections 2, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow up questionnaire
	Additional risk minimization measures: Healthcare professional guide Caregiver information guide	**Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Cardiac adverse events	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3 PL Sections 2, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow up questionnaire
	Additional risk minimization measures: None	**Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Use in patients with anti-AAV9 antibody titres > 1:50	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:

Safety concern	Risk minimization measures	Pharmacovigilance activities
and higher vector loads required	**Additional risk minimization measures**: None	None **Additional pharmacovigilance activities**: None
Dorsal root ganglia toxicity	**Routine risk minimization measures**: SmPC Section 5.3 **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow up questionnaire **Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Tumorigenicity due to chromosomal integration	**Routine risk minimization measures**: SmPC Sections 4.4, 5.1 PL Section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Long-term efficacy of onasemnogene abeparvovec therapy	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

13 Part VI: Summary of the risk management plan for Zolgensma (onasemnogene abeparvovec)

This is a summary of the risk management plan (RMP) for Zolgensma. The RMP details important risks of Zolgensma, how these risks can be minimized, and how more information will be obtained about Zolgensma's risks and uncertainties (missing information).

Zolgensma's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zolgensma should be used.

This summary of the RMP for Zolgensma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zolgensma's RMP.

13.1 Part VI: I. The medicine and what it is used for

Zolgensma is authorised for the treatment of:

- Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron 1 (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 survival motor neuron 2 (SMN2) gene.

It is a gene replacement therapy and it is given by intravenous route. For patients who weigh 2.6 to 21.0 kg, the intravenous dosage is determined by patient body weight with a nominal recommended dose of 1.1×10^{14} vg/kg.

Further information about the evaluation of Zolgensma's benefits can be found in Zolgensma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Zolgensma, together with measures to minimize such risks and the proposed studies for learning more about Zolgensma's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment (if applicable) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zolgensma's is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Zolgensma are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zolgensma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events • Use in patients with anti-AAV9 antibody titers > 1:50 and higher vector loads required • Dorsal root ganglia toxicity • Tumorigenicity due to chromosomal integration
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy • Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important identified risk: Hepatotoxicity

Evidence for linking the risk to the medicine	**Clinical trials**: Transaminase elevations have been observed without association with clinical signs or symptoms. **Early access programs and post-marketing reports**: Adverse events of transaminase elevations are commonly reported following onasemnogene abeparvovec administration. In the post-marketing setting, cases of ALF have been reported, some of which had fatal outcomes.
Risk factors and risk groups	Patients with impaired liver function

	Data from a small study in children weighing ≥8.5 kg to ≤21 kg (aged approximately 1.5 to 9 years), indicate a higher frequency of AST or ALT elevations (in 23 out of 24 patients) compared with frequencies of AST/ALT elevations observed in other studies in patients weighing <8.5 kg (in 31 out of 99 patients)
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8. 5.2, and 5.3 Package leaflet (PL) Sections 2, 3, 4 **Additional risk minimization measures**: Healthcare professional guide Caregiver information guide
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: Transient thrombocytopenia

Evidence for linking the risk to the medicine	**Clinical trials**: Transient thrombocytopenia was observed in onasemnogene abeparvovec clinical studies. In most cases, the lowest platelet value occurred the first week following onasemnogene abeparvovec infusion. **Early access programs and post-marketing reports**: Adverse events of thrombocytopenia or decreased platelet counts are commonly reported after onasemnogene abeparvovec administration. These events are generally not clinically significant. Post-marketing cases with platelet counts < 50 × 10^9/L and <25 x 10^9/L have been reported to occur within three weeks following onasemnogene abeparvovec administration.
Risk factors and risk groups	In a study (COAV101A12306) including 24 children weighing ≥8.5 kg to ≤21 kg (aged approximately 1.5 to 9 years), thrombocytopenia was observed in 20 out of 24 patients.
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 4 **Additional risk minimization measures**: Caregiver information guide
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-4 Important identified risk: Thrombotic microangiopathy

Evidence for linking the risk to the medicine	Cases of TMA were reported in 23 patients in the post-marketing setting, early access programs, and the registry, cumulatively up to DLP 23-May-2022. Of these, in 12 patients, diagnosis of TMA was supported by available clinical details. All 12 confirmed TMA cases were reported within 1-2 weeks post onasemnogene abeparvovec infusion. TMA is characterized by acute and/or chronic uncontrolled dysregulation and/or excessive activation of the alternative pathway of complement, and its etiology can be genetic or acquired, occurring in

	both children and adults. TMA is a life-threatening condition, with fatal outcomes reported. In 2020, the incidence of TMA in children is estimated to be three cases/million/year. Although the incidence of TMA in children with SMA is unknown, recent literature suggests coagulation abnormalities can occur inherently in this population. A genetic predisposition to TMA has been associated with mutations in the genes encoding complement factor H, complement factor I, complement factor B, membrane cofactor protein, C3, and thrombomodulin, as well as autoantibodies against complement factor H or complement factor I have been reported. In rare conditions, atypical hemolytic uremic syndrome is due to mutation in diacyglycerol kinase ε or deficiency of cobalamin C. Acquired TMA can occur in association with a wide range of viral, bacterial, fungal, and parasitic infections, although it is frequently unclear if this is a direct effect of the pathogen, an adverse reaction to the treatment of an infection, or a trigger that unmasks a latent complement defect. Furthermore, encapsulated organisms have been identified as a trigger; capsular polysaccharide is a critical virulence factor that enables immune evasion. Although an exact mechanism for TMA is unknown, given its rarity in the general population, the number of cases reported for the patients with the rare disease (SMA), and similar pattern of time to onset of TMA, a causal association between onasemnogene abeparvovec and TMA is plausible.
Risk factors and risk groups	Infections and vaccinations
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8 PL Sections 2, 4 **Additional risk minimization measures**: Healthcare professional guide Caregiver information guide
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-5 Important potential risk: Cardiac adverse events

Evidence for linking the risk to the medicine	**Non clinical**: Cardiac degeneration, fibrosis and atrial thrombosis were reported in non-clinical toxicity GLP studies in mice (dosing in mice was higher compared to human dosing). **Clinical**: Cardiac-related non-clinical findings have not been observed in humans. Minor transient increases in CK-MB and troponin I were reported with no associated clinical sequelae. Cases of tachycardia and bradycardia also occurred. However, the significance of elevated cardiac enzymes or changes in heart rates cannot be determined given the available data.
Risk factors and risk groups	Underlying cardiac abnormalities
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3

	PL Sections 2, 4 **Additional risk minimization measures**: None
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-6 Important potential risk: Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required

Evidence for linking the risk to the medicine	**Clinical**: Patients with AAV9 titres > 1:50 have not been studied in onasemnogene abeparvovec clinical studies. After administration of onasemnogene abeparvovec, increases in anti-AAV9 antibody titres were observed. This is considered an expected response, and there were no apparent relationships between anti-AAV9 antibody titre and safety or efficacy. It is not known whether administration of the onasemnogene abeparvovec vector represents a risk for patients with anti-AAV9 antibodies at higher titres.
Risk factors and risk groups	Patients with anti-AAV9 titres > 1:50 prior to administration of onasemnogene abeparvovec.
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8 **Additional risk minimization measures**: None
Additional pharmacovigilance activities	See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-7 Important potential risk: Dorsal root ganglia toxicity

Evidence for linking the risk to the medicine	**Clinical**: No adverse events suggestive of ganglionopathy were observed in patients treated with onasemnogene abeparvovec from clinical trials, early access programs, registry and post-marketing clinical experience in whom treatment with steroids was administered. All available autopsy reports of fatal cases in the post marketing setting are being monitored for evidence of DRG toxicity. A limited number of autopsy reports received for the post-marketing cases until 23 May 2022 did not indicate histological evidence of DRG toxicity. **Non-clinical**: In cynomolgus monkeys, i.t. and i.v. administration of onasemnogene abeparvovec has been associated with clinically silent (asymptomatic) microscopic changes in the dorsal root ganglia (DRG) and/or trigeminal ganglia. The findings in the DRG (at all levels) and/or trigeminal ganglia included mononuclear cell inflammation, neuronal degeneration, satellitosis, and/or neuronal necrosis. These non-clinical DRG findings have not been confirmed in patients from both clinical trials as well as post-marketing experience. Based on data accumulated so far from the GLP non-human primate studies at terminal intervals up to 6 weeks post dose, the OAV101-related DRG finding is reclassified from “DRG cell inflammation” to “DRG toxicity” given that the microscopic findings are generally characterized by mononuclear cell inflammation, neuronal degeneration, satellitosis, neuronal loss, gliosis and/or axonal

	degeneration. In addition, secondary changes in the spinal cord and peripheral nerves of axon degeneration have been observed.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures**: SmPC Section 5.3 **Additional risk minimization measures**: None
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-8 Important potential risk: Tumorigenicity due to chromosomal integration

Evidence for linking the risk to the medicine	There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Onasemnogene abeparvovec is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Rare instances of random vector integration into human DNA are possible with recombinant AAV. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections 4.4, 5.1 PL Section 2 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-9 Missing information: Long-term efficacy of onasemnogene abeparvovec therapy

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None
Additional pharmacovigilance activities	AVXS-101-LT-001 and AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-10 Missing information: Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None
Additional pharmacovigilance activities	None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

Table 13-11 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
AVXS-101-RG-001: A prospective long-term registry of patients with a diagnosis of SMA (RESTORE)	To assess long-term outcomes in patients with a diagnosis of SMA.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-12 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
AVXS-101-LT-001: Long-term follow-up study for patients from AVXS-101-CL-101 (START)	To collect long-term follow-up safety data of patients with SMA Type 1 who were treated with onasemnogene abeparvovec in the AVXS-101-CL-101 study.
AVXS-101-LT-002: A long term follow up study of patients in the clinical trials for SMA Type 1 Delivering onasemnogene abeparvovec	To collect long term, follow up safety and efficacy data in patients with SMA who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Hepatotoxicity

Elevated Liver Enzymes (v 4.0; Mar-2024)

NOVARTIS

Argus ID # _____

Manufacturer Receipt Date (dd/mmm/yyyy) ____/_____/_____

Zolgensma (onasemnogene abeparvovec)
Elevated Liver Enzymes Targeted Follow-up Checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed. By providing as detailed information as possible, you can make a useful contribution to the safety of Zolgensma.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of Zolgensma administration	Dose administered	SMA type/ SMA status

1. **Please provide up to the last two liver test results *PRIOR* to administration of Zolgensma. Please attach anonymized copy of relevant liver test reports, if available.**

Tests	Date	Value	Expected Normal range	Not performed
AST				☐
ALT				☐
Bilirubin total				☐
Albumin				☐
Prothrombin time				☐
Partial thromboplastin time				☐
International normalized ratio				☐
AST				☐
ALT				☐
Bilirubin total				☐
Albumin				☐
Prothrombin time				☐
Partial thromboplastin time				☐
International normalized ratio				☐

2. **Please provide liver test results *AFTER* administration of Zolgensma.**

	Test	Date	Value	Expected Normal range	Not performed
First Liver test above normal range after administration of Zolgensma	AST				☐
	ALT				☐
	Bilirubin total				☐
Highest liver test after administration of Zolgensma	AST				☐
	ALT				☐
	Bilirubin total				☐

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Argus ID # _____

Manufacturer Receipt Date (dd/mmm/yyyy) ____/____/____

	Test	Date	Value	Expected Normal range	Not performed
Resolution of liver tests to within normal range or last available result	AST				☐
	ALT				☐
	Bilirubin total				☐
In case of hepatic injury, further testing is recommended	Albumin				☐
	Prothrombin time				☐
	Partial thromboplastin time				☐
	International normalized ratio				☐

3. **Did the patient present with any of the following signs or symptoms? Check all that apply**

☐ Jaundice ☐ Ascites ☐ Asterixis (flapping tremor)
☐ Dark urine ☐ Fever ☐ Altered mental status
☐ Pale stool ☐ Fatigue ☐ Abdominal pain (incl. location)
☐ Pruritus ☐ Bleeding (specify location) ☐ Anorexia or loss of appetite
☐ Nausea or vomiting ☐ Other (specify) ☐ None
☐ Hepatosplenomegaly

Please provide further details below: _____

4. **Were any of the following diagnostic tests performed?**

Tests	Before administration of Zolgensma		After administration of Zolgensma		Normal range (if applicable)
	Date	Result	Date	Result	
Serology & PCR testings for Hepatitis A, B, C &/or E virus					
Abdominal or hepatobiliary ultrasound					
Abdominal CT scan					
Liver biopsy					
Other (specify)					

5. Was treatment of the elevated liver enzymes required? ☐ Yes ☐ No

If YES, please describe treatments and outcomes of the events:

6. **Please provide the actual baseline anti-AAV9 antibody titers**

Test	Date	Result	Not available
Anti-AAV9 antibody			☐

NOVARTIS

Argus ID # _____

Manufacturer Receipt Date (dd/mmm/yyyy) ____/_____/_____

7. Please provide details of prednisolone administration below

Drug	Dose	Date started	Date stopped	Reason for stopping/restarting

8. Was Nusinersen administered? ☐ Yes ☐ No If yes please provide information.

Dose	Amount administered	Date
1		
2		
3		
4		
5		
6		
7		

9. Please provide the interval between last Nusinersen dose and Zolgensma administration: _____

_____

10. Please list any concomitant therapies below

Therapy	Indication	Dose	Start date	Stop date	Contribution to elevated liver enzymes Yes/No

11. Please list any concomitant medical conditions below

Condition	Start date	Stop date	Contribution to elevated liver enzymes Yes/No

12. Please provide any other relevant information

_____
_____
_____
_____
_____
_____
_____
_____

Transient thrombocytopenia

Decreased platelets (v 3.0; Mar-2024)

NOVARTIS

Argus ID # _____

Manufacturer Receipt Date (dd/mmm/yyyy) ____/_____/_____

Zolgensma (onasemnogene abeparvovec)
Decreased Platelet Count Targeted Follow-up Checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed. By providing as detailed information as possible, you can make a useful contribution to the safety of Zolgensma.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of Zolgensma administration	Dose administered

1. **Please provide the information below related to the event of decreased platelet count. Please attach anonymized copy of relevant platelet reports, if available.**

	Date	Platelet Count	Expected Normal range	Not available
Platelet count before administration of Zolgensma				☐
First platelet count below normal range after administration of Zolgensma				☐
Lowest platelet count after administration of Zolgensma				☐
Resolution of platelet count to within normal range or last available platelet count				☐

2. **Were there any bleeding events associated with the decreased platelet count?** ☐Yes ☐No

If YES, please describe: _____

3. **Was there any concomitant abnormality in other hematological parameters** ☐Yes ☐No

If YES, please describe with date and results: _____

4. **Was blood and/or platelet transfusion required for decreased platelet count?** ☐Yes ☐No

If YES, please describe treatment and outcome of the event: _____

5. **Please provide the actual baseline anti-AAV9 antibody titers**

Test	Date	Result	Not available
Anti-AAV9 antibody			☐

6. **Was Nusinersen administered?** ☐ **Yes** ☐ **No If yes please provide information below**

Dose	Amount administered	Date
1		
2		
3		
4		
5		
6		
7		

NOVARTIS

Argus ID # _____

Manufacturer Receipt Date (dd/mmm/yyyy) ____/_____/_____

7. **Please provide the interval between the last Nusinersen dose and Zolgensma administration:** _____

_____

8. **Please list any concomitant therapies below**

Therapy	Indication	Dose	Start date	Stop date	Contribution to decreased platelet count Yes/No

9. **Please list any concomitant medical conditions below**

Condition	Start date	Stop date	Contribution to decreased platelet count Yes/No

10. **Please provide any other relevant information**

_____
_____
_____
_____
_____

Thrombotic microangiopathy

Thrombotic microangiopathy (v 3.0; Mar-2024)

NOVARTIS

ARGUS ID #: _____

Manufacture Receipt Date (dd/mmm/yyyy): _____/_____/_____

Zolgensma (onasemnogene abeparvovec)
Thrombotic microangiopathy (TMA) Targeted Follow-up Checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed. By providing as detailed information as possible, you can make a useful contribution to the safety of Zolgensma.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of Zolgensma administration	Dose administered	SMA type/ SMA status

Was there any consanguinity in the parents? ☐ Yes ☐ No ☐ Unknown

Any siblings with SMA? ☐ Yes ☐ No

1. Please provide the following baseline values and tests PRIOR to administration of Zolgensma (if available)

	Date	Value/Results	Reference Range	Not performed
Anti-AAV9 antibody titers				☐
Platelet Count				☐
Hemoglobin				☐
Creatinine				☐
Blood pressure		...../.....		☐
Kidney ultrasound				☐

2. Conditions and events description

Conditions/Events	2 months before administration of Zolgensma			After administration of Zolgensma		
		Date	Description		Date	Description
TMA (or any of its components: thrombocytopenia, anemia or kidney impairment)	☐ Yes ☐ No			☐ Yes ☐ No		
Diarrhea	☐ Yes ☐ No			☐ Yes ☐ No		
Vomiting	☐ Yes ☐ No			☐ Yes ☐ No		
Fever	☐ Yes ☐ No			☐ Yes ☐ No		
Infection	☐ Yes ☐ No			☐ Yes ☐ No		
Bleeding	☐ Yes ☐ No			☐ Yes ☐ No		
Any illnesses (define pathogen):	☐ Yes ☐ No			☐ Yes ☐ No		

3. What was the patient's blood pressure AFTER administration of Zolgensma? ☐ NA

NOVARTIS

ARGUS ID #: _____

Manufacture Receipt Date (dd/mmm/yyyy): _____/_____/_____

Date	Systolic blood pressure reading	Diastolic blood pressure reading

4. Please provide all available lab values, all complement values and diagnostic tests AFTER administration of Zolgensma.

Tests	Dates	Values (highest or lowest values) or exam results	References Range if applicable	Not performed
Platelet Count				☐
Hemoglobin				☐
Schistocytes				☐
LDH				☐
Haptoglobin				☐
Serum Creatinine				☐
Serum BUN				☐
Urine Protein				☐
Urine Creatinine				☐
Shiga toxin E. coli				☐
Complement (C3)				☐
Complement (C4)				☐
Bb fragment concentration				☐
Soluble C5b-9				☐
CH50eq				☐
Alternative pathway functional assay				☐
Hemolytic assay				☐
FH autoantibody				☐

NOVARTIS

ARGUS ID #: _____

Manufacture Receipt Date (dd/mmm/yyyy): _____/_____/_____

Tests	Dates	Values (highest or lowest values) or exam results	References Range if applicable	Not performed
Factor B				☐
Factor H				☐
Factor I				☐
ADAMTS-13				☐
Kidney ultrasound				☐

5. Was genetic testing for TMA done? ☐ Yes ☐ No If YES, please provide dates and results:

_____

_____

_____

6. Was Nusinersen administered? ☐ Yes ☐ No If yes please provide information.

Dose	Amount administered	Date
1		
2		
3		
4		
5		
6		
7		

7. Please provide the interval between last Nusinersen dose and Zolgensma administration: _____

_____

8. Please provide details of prednisolone (or equivalent corticosteroid) administration.

Drug	Dose	Date started	Date stopped	Reason for stopping/restarting

9. Please list any concomitant therapies/medications for the treatment of TMA or concurrently administered during TMA below

Therapy/Medication	Indication	Dose	Start date	Stop date	Ongoing
					☐
					☐
					☐
					☐
					☐
					☐
					☐
					☐

NOVARTIS

ARGUS ID #: _____

Manufacture Receipt Date (dd/mmm/yyyy): _____/_____/_____

10. Please describe any other relevant information.

_____
_____
_____

_____
_____

_____
_____

Cardiac adverse events

Cardiac adverse events (v 3.0; Mar-2024)

NOVARTIS

Argus ID # _____
Manufacturer Receipt Date (dd/mmm/yyyy) / /

Zolgensma (onasemnogene abeparvovec)
Cardiac Adverse Events Targeted Follow-up Checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed. By providing as detailed information as possible, you can make a useful contribution to the safety of Zolgensma.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of Zolgensma administration	Dose administered	SMA type/ SMA status

1. **Cardiac Event Description:**

Diagnosis	Date of diagnosis	Cause of cardiac event	Treatment	Outcome
				☐ Resolved ☐ Improving ☐ Not resolved ☐ Fatal

Please attach anonymized copy of cardiologist's reports, if available.

2. **Did the patient have any of the following symptoms and signs?**

☐ Tachycardia or tachyarrhythmia
☐ Bradycardia or bradyarrhythmia
☐ Supine cough
☐ Chest pain
☐ Hypotension
☐ Fatigue
☐ Palpitations
☐ Dyspnoea
☐ Dizziness
☐ Syncope
☐ Edema
☐ Other:.....

3. **Please provide a brief description of the following investigations. Please also provide anonymized reports.**

Investigations	Before administration of Zolgensma		After administration of Zolgensma		At time of the event		At resolution of the event or last available results	
	Date	Results	Date	Results	Date	Results	Date	Results
ECG								
Holter								
Chest X Ray								
Echocardiogram								

NOVARTIS

Argus ID # _____
Manufacturer Receipt Date (dd/mmm/yyyy) / /

Investigations	Before administration of Zolgensma		After administration of Zolgensma		At time of the event		At resolution of the event or last available results	
	Date	Results	Date	Results	Date	Results	Date	Results
Electrolytes (values, normal range)								
Troponin1 (values, normal range)								
CK-MB (values, normal range)								
Other								

4. **Medical history _ Concomitant Conditions**

Condition	Description of cardiac disease	Start date	Stop date
Congenital heart disease (specify please)			
Arrhythmia (specify please)			
Hypertension			
Pericarditis			
Infection			
Other (concomitant conditions which could contribute to cardiac event)			
Family health history of heart disease			

5. **Please provide the actual baseline anti-AAV9 antibody titers**

Test	Date	Result	Not available
Anti-AAV9 antibody			☐

6. **Was Nusinersen administered?** ☐ **Yes** ☐ **No If yes please provide information**

Dose	Amount administered	Date
1		
2		
3		
4		
5		
6		
7		

7. **Please provide the interval between last Nusinersen dose and Zolgensma administration:** _____

NOVARTIS

Argus ID #_____
Manufacturer Receipt Date (dd/mmm/yyyy) / /

8. **Concomitant medications**

Please list any concomitant therapies below

Therapy	Indication	Dose	Start date	Stop date	Contribution to cardiac event Yes/No

9. **Please provide any other relevant information below.**

Dorsal root ganglia toxicity

Sensory neuronopathies (v2.0; Mar-2024)

NOVARTIS

ARGUS ID #:_____

Manufacture Receipt Date (dd/mm/yyyy): _____/_____/_____

Zolgensma (onasemnogene abeparvovec)
Sensory Neuronopathies Targeted Follow-up Checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed. By providing as detailed information as possible, you can make a useful contribution to the safety of Zolgensma.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of Zolgensma administration	Dose administered	SMA type/ SMA status

1. **Event Description:**

Did the patient present with any of the following signs or symptoms? Check all that apply

- ☐ Paresthesia, Dysesthesia
- ☐ Hyperesthesia
- ☐ Hypoesthesia
- ☐ Thermesthesia
- ☐ Sensory ataxia with balance disorders *(please specify)*
- ☐ Loss of proprioception/vibratory sense
- ☐ Absent tendon reflex
- ☐ Areflexia
- ☐ Anesthesia
- ☐ Pain
- ☐ Distal sensory disorders *(please specify)*
- ☐ None of the above
- ☐ Autonomic disorders *(please specify and describe below the following symptoms: orthostatic hypotension, constipation, diarrhea, bladder disturbances, abnormal sweating and/or and pupil abnormalities)*

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What pattern of neuropathy is the patient experiencing? Check all that apply

- ☐ Mononeuropathy
- ☐ Polyneuropathy
- ☐ Symmetric
- ☐ Asymmetric
- ☐ Proximal
- ☐ Distal

Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates and results

- ☐ Electromyoneurography (EMNG)
- ☐ Nerve conduction studies
- ☐ Neurological examination (sensory exam, motor exam, deep tendon reflexes)
- ☐ Autonomic testing
- ☐ MRI of spinal cord
- ☐ CSF analysis
- ☐ Skin biopsy
- ☐ None of the above

Were any of the additional tests performed? Check all that apply and please specify which test(s), dates and results

- ☐ Lyme (B. burgdorferi) titer
- ☐ Serum B6, B12, folic acid, thiamine
- ☐ Serum autoantibodies (antinuclear antibodies, anti-Ro and anti-La, antigliadin and antitransglutaminase)
- ☐ Serologic testings (Hepatitis, HIV, CMV, EBV, HTLV-1, EBV, VZV, Zika virus, leprosy)
- ☐ Testing for anti–trisulfated heparin disaccharide and anti–fibroblast growth factor receptor 3 antibodies.
- ☐ Whole-body PET-CT in case of cancer diagnosis, followed by diagnostic biopsy

2. **Patient History:**

Does the patient have any relevant medical history?

Has the patient recently taken any of the following? Check all that apply

- ☐ Interferon therapy
- ☐ Antimicrobials (e.g. ciprofloxacin, metronidazole)
- ☐ Immunosuppressant or antineoplastic drugs (e.g. cisplatin, vincristine)
- ☐ Nucleoside analogs (for HIV, Hepatitis B, C)
- ☐ Pyridoxine (vitamin B6)
- ☐ Cardiovascular drugs (e.g. enalapril, hydralazine)
- ☐ None of the above

Please provide the actual baseline anti-AAV9 antibody titers

NOVARTIS

ARGUS ID #:_____

Manufacture Receipt Date (dd/mm/yyyy): _____/_____/_____

Test	Date	Result	Not available
Anti-AAV9 antibody			☐

Was Nusinersen administered? ☐ Yes ☐ No If yes please provide information.

Dose	Amount administered	Date
1		
2		
3		
4		
5		
6		
7		

Please provide the interval between last Nusinersen dose and Zolgensma administration: _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Key messages of the additional risk minimization measures
Healthcare Professional Information Pack

SmPC

Healthcare professional guide

The healthcare professional guide shall contain the following key messages:

- Before the start of treatment:
  - The HCP should evaluate the patient's vaccination schedule;
  - Inform the caregiver(s) about the main risks with Zolgensma and their signs and symptoms, including TMA, hepatic failure and thrombocytopenia; about the need for regular blood sampling; the importance of corticosteroid medication; practical advice concerning bodily waste disposal;
  - Inform the caregiver(s) of the need for increased vigilance in the prevention, monitoring, and management of infection before and after Zolgensma infusion;
  - Patients should be tested for the presence of AAV9 antibodies.
- At the time of infusion:
  - Check if the overall health status of the patient is suitable for the infusion (e.g. resolution of infections) or if a postponement is warranted;
  - Check that corticosteroid treatment was started before the infusion of Zolgensma;
- After infusion:
  - The corticosteroid treatment should continue for at least 2 months; and not be tapered until AST/ALT are less than 2 x ULN, and all other assessments, e.g. total bilirubin, return to normal range;
  - Close and regular monitoring (clinical and laboratory) of the individual patient course should be performed for at least 3 months;
  - Prompt assessment of patients with worsening liver function tests and/or signs or symptoms of acute illness;
  - If patients do not respond adequately to corticosteroids, or if liver injury is suspected, HCP should consult a paediatric gastroenterologist or hepatologist;
  - If TMA is suspected, a specialist should be consulted.

Patient Information Pack

Package Leaflet

Caregiver information guide

The patient information pack shall contain the following key messages:

- What is SMA.
- What is Zolgensma and how it works.

- Understanding the risks of Zolgensma.
- Treatment with Zolgensma: important information before, on the day of infusion and after treatment, including when to seek medical attention.
- It is recommended that patients present an adequate overall health status (e.g. hydration and nutritional status, absence of infection) prior to Zolgensma treatment, otherwise treatment may need to be postponed.
- Zolgensma may increase the risk of abnormal clotting of blood in small blood vessels (thrombotic microangiopathy). Cases generally occurred within the first two weeks after onasemnogene abeparvovec infusion. Thrombotic microangiopathy is serious and may lead to death. Tell your doctor immediately if you notice signs and symptoms such as bruising, seizures or decrease in urine output. Your child will have a regular blood test to check any decrease of platelets, the cells responsible for clotting, for at least 3 months after treatment. Depending on the values and other signs and symptoms, further evaluations may be required.
- Zolgensma can lower blood-platelet counts (thrombocytopenia). Cases generally occurred within the first three weeks after onasemnogene abeparvovec infusion. Possible signs of a low blood-platelet count you need to look out for after your child is given Zolgensma include abnormal bruising or bleeding. Speak to your doctor if you see signs such as bruising or bleeding for longer than usual if your child has been hurt.
- Zolgensma can lead to an increase in enzymes (proteins found within the body) produced by the liver. In some cases, Zolgensma can affect the function of the liver and lead to injury of the liver. Injury to the liver can lead to serious outcomes, including liver failure and death. Possible signs you need to look out for after your child is given this medicine include vomiting, jaundice (yellowing of the skin or of the whites of the eyes), or reduced alertness. Tell your child's doctor straightaway if you notice your child develops any symptoms suggestive of injury to the liver. Your child will have a blood test to check how well the liver is working before starting treatment with Zolgensma. Your child will also have regular blood tests for at least 3 months after treatment to monitor for increases in liver enzymes. Depending on the values and other signs and symptoms, further evaluations may be required.
- Your child will be given a corticosteroid medicine such as prednisolone before treatment with Zolgensma, and for about 2 months or longer after Zolgensma treatment. The corticosteroid medicine will help manage effects of Zolgensma such as increase in liver enzymes that your child could develop after treatment with Zolgensma.
- Tell your doctor in the event of vomiting before or after treatment with Zolgensma, to make sure that your child does not miss corticosteroid dosing.
- Before and after treatment with Zolgensma it is important to prevent infections by avoiding situations that may increase the risk of the child getting infections. Caregivers and close contacts with the patient should follow infection prevention practices (e.g. hand hygiene, coughing/sneezing etiquette, limiting potential contacts). Inform the doctor straightaway in case of signs and symptoms suggestive of infection, such as respiratory infection (coughing, wheezing, sneezing, runny nose, sore throat or fever) prior to infusion as the infusion may need to be delayed until the infection is resolved, or after treatment with Zolgensma as it may lead to medical complications that may require urgent medical attention.

- Useful further information (supportive care, local associations).
- Contacts of the physician/prescriber.