NOVARTIS

Patient Safety & Pharmacovigilance

Onasemnogene abeparvovec

OAV101A / OAV101B

EU Safety Risk Management Plan

Active substance (INN or common name):	Onasemnogene abeparvovec
Products concerned (brand names):	Zolgensma® and Itvisma®
Document status:	Final
Version number:	5.3
Data lock point for this RMP:	27-May-2025
Date of final sign off:	10-Apr-2026

Rationale for submitting an updated RMP:

This updated EU Safety Risk Management Plan (RMP) version 5.3 has been prepared in response to CAT day 189 list of questions received during the review of the Itvisma European Union (EU) Marketing Authorization Application (MAA) procedure (EMEA/H/C/006498).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v5.2
Part I	No changes
Part II	Module SVII: Table 8-3 updated the peak Itvisma vector shedding in stool details. Table 8-6 Added missing information 'long term safety of onasemnogene abeparvovec therapy for Itvisma. 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 updated for Zolgensma only. Section 8.3.1.6 Updated risk name Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy. Table 8-17 Updated evidence source details of Tumorigenicity due to chromosomal integration risk. Table 18-19: Added Long term safety of onasemnogene abeparvovec therapy for Itvisma. Table 9-1 Updated risk name Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy and added Long-term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only) .
Part III	Updated the checklist name from Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy. Table 10-1 Updated risk name Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy and added Long-term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only). Removed COAV101B12401 and added SMA registries feasibility assessment for Itvisma.
Part IV	No changes.
Part V	Table 12-1 Updated risk name Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy and added Long-term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only). Section 12.2 Updated safety areas of concern in the Additional Risk Minimization Measure "Educational materials". Table 12-2 updated Additional Risk Minimization Measure details for risks Transient thrombocytopenia and Dorsal root ganglia toxicity/peripheral sensory neuropathy. Long-term safety of onasemnogene abeparvovec therapy is added as missing information for Itvisma. Updated additional risk minimization measures (Healthcare professional guide) for Dorsal root ganglia toxicity/peripheral sensory neuropathy and Thrombocytopenia. Updated additional risk minimization measures Patient/patient's caregiver information guide for Dorsal root ganglia toxicity/peripheral sensory neuropathy. Updated additional pharmacovigilance activities for Long-term safety of onasemnogene abeparvovec therapy. Removed COAV101B12401 and added SMA registries feasibility assessment for Itvisma.

Part	Major changes compared to RMP v5.2
Part VI	Updated Table 13-1 Updated risk name Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy. Added Long-term safety of onasemnogene abeparvovec therapy for Itvisma. Table 13-3 Updated additional risk minimization measures details. Table 13-7 updated risk name and additional risk minimization measures details. Removed COAV101B12401 and added SMA registries feasibility assessment for Itvisma. Table 13-8 updated evidence detail for Tumorigenicity due to chromosomal integration risk. Added SMA registries feasibility assessment. Table 13-10 Added missing information Long-term safety of onasemnogene abeparvovec therapy for Itvisma. Table 13-13 Removed COAV101B12401 and added SMA registries feasibility assessment.
Part VII	Annex 4: Updated checklist name from Dorsal root ganglia toxicity to Dorsal root ganglia toxicity/peripheral sensory neuropathy risk. Annex 6: Updated include key safety messages for peripheral sensory neuropathy.

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMEA/H/C/004750/IB/0050

Date of approval: 04-Jun-2024

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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List of abbreviations

AAV	Adeno-associated virus
AAV9	Adeno-associated virus serotype 9
AAVS1	Adeno-associated virus integration site 1
AE	Adverse event
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
BLQ	Below the Limit of Quantification
CCIT	Container closure integrity testing
CK-MB	Creatine kinase isoenzyme - muscle/brain
CMC	Chemistry, Manufacturing, and Controls
CNS	Central nervous system
CSF	Cerebrospinal fluid
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
EEA	European Economic Area
EFD	Embryo-foetal development
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FEED	Fertility and Early Embryonic Development
FEV1	Forced Expiratory Volume in 1 second
FVB	Friend leukemia virus B
FVC	Forced Vital Capacity
HCP	Healthcare Professional
HIV	Human immunodeficiency virus
HLT	High level term
INN	International non-proprietary name
ISA	Integration Site Analysis
ISTA	International Safe Transit Association
IT	Intrathecal
IV	Intravenous
IVIG	Intravenous Immunoglobulin
LTFU	Long Term Follow-Up

MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCH	Nationwide Children's Hospital
NEC	Not Elsewhere Classified
NHP	Non-Human Primate
NIV	Non-Invasive Ventilation
NOAEL	No Observed Adverse Effect Level
PL	Package leaflet
PSAF	Pooled Safety Analysis Set
PSUR	Periodic Safety Update Report
PT	Preferred Terms
PT(INR)	Prothrombin Time (International Normalized Ratio)
QP	Qualified Person
QPPV	Qualified person for pharmacovigilance
rAAV	Recombinant AAV
RNA	Ribonucleic acid
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
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
SNAP	Sensory nerve action potential
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
TMA	Thrombotic microangiopathy
ULN	Upper Limit of Normal
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	2
Invented name in the European Economic Area (EEA)	Zolgensma®, Itvisma®
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 spinal muscular atrophy (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. The mechanism of action of onasemnogene abeparvovec is the delivery of SMN cDNA encoding a functional, full-length SMN protein into target cells, correcting the genetic root defect in SMA. The vector genome persists in cells, including neurons, as episomal monomeric and concatemeric circles in a structure consistent with that of chromatin, resulting in a sustained and consistent supply of SMN protein. 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, IV injections of AAV9 led to early and persistent transgene expression and improvement in survival and motor function. Zolgensma treatment has resulted in profound improvement in survival and achievement of motor milestones in patients with SMA, as well as reducing the need for respiratory or nutritional support. 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	Zolgensma: [Current approved SmPC for IV] Itvisma: [Proposed SmPC for IT]
Indications in the EEA	**Current:** Zolgensma: 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: Itvisma: Itvisma is indicated for the treatment of 5q SMA with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older.
Dosage in the EEA	**Current**: Zolgensma: 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} vector genomes (vg)/kg. An immune response to the AAV9 capsid will occur after administration of Zolgensma, thus patients should not be re-dosed with onasemnogene abeparvovec. Zolgensma is for a single treatment only.
	Proposed: Itvisma: Itvisma is administered as a single dose of 1.2×10^{14} (vg) for intrathecal use. Because the treatment persists in nondividing cells, patients previously treated with onasemnogene abeparvovec (any route of administration) should not be treated with Itvisma.
Pharmaceutical form and strengths	**Current**: Zolgensma: When thawed, Zolgensma is a clear to slightly opaque, colourless to faint white solution. Each vial contains Zolgensma 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: Itvisma: Solution for injection. When thawed, Itvisma is a clear to slightly opaque, colourless to faint white solution with a pH of 7.7 - 8.3 and osmolality of 390 - 430 mOsm/kg. Each single-dose vial contains 1.2×10^{14} vg of Itvisma in 3 mL of solution. Itvisma has a nominal concentration of 4×10^{13} vg/mL, and each vial contains an extractable volume of not less than 3 mL.
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

Itvisma is indicated for the treatment of 5q SMA with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older.

The naming convention Zolgensma and Itvisma is used throughout the document when describing the intravenous and intrathecal formulation. When information applies to both products, the generic name onasemnogene abeparvovec is used.

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. Historically, several phenotypes of SMA were 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).

Newborn genetic screening and early treatment have changed the clinical course of SMA, dramatically improving outcomes for SMA patients. With the development of disease-modifying treatments and the resulting dynamic clinical picture of the treated SMA patients, this historical classification of SMA is no longer appropriate based on the treatment paradigm shift with disease modifying therapy resulting in individuals with SMA gaining more motor milestones and function than the predicted historical classification (Wirth et al 2020).

Incidence:

SMA studies 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).

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.

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* Mar2016	Rare disease prevalence per 10,000 Mar2016
1	ORPHA83330	1 / 80,000	0.125
2	ORPHA83418	1 / 70,000	0.142
3	ORPHA83419	1 / 375,000	0.027
4	ORPHA83420	1 / 300,000	0.033

*Orphanet

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

Type	Age at symptom onset	Maximum motor function	Life expectancy	SMN2 copy number
4	> 35 years	Slow decline	Normal	4-8

Source: Adapted from Kolb and Kissel 2011.
Bold = predominant SMN2 copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

Newborn genetic screening and early treatment have changed the clinical course of SMA, dramatically improving outcomes for SMA patients. For this reason, the historical classification of SMA based primarily on Type, age of onset, and SMN copies is no longer appropriate and a classification based on gained motor milestones and function came in use (Wirth et al 2020).

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 IT 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. A warning has been added recently regarding the risk of arachnoiditis associated with the lumbar puncture procedure. The SmPC now advises that an MRI should be performed to confirm the diagnosis and the extent of the inflammation. If arachnoiditis is identified, the use of the injection site should be avoided until local inflammation has been ruled out. Additionally, "Arachnoiditis" has been added to the list of adverse drug reactions with a frequency not known, based on postmarketing review (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 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 SMA (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, disability present as 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).

In adult SMA patients, the respiratory function is frequently impaired, but generally stable, and significantly correlated with motor function and disease severity. Vicino et al 2023 assessed respiratory function in a cohort of 145 SMA patients without treatment in a multi-center cross-sectional study. Of these patients 37% and 31% had abnormal (<80%) values of FVC and FEV1,

respectively. A total of 14% needed non-invasive ventilation (NIV) started at median age of 21 (range 4 - 68).

Adults with SMA had a higher and earlier prevalence of a variety of morbidities across physiological systems and mental health disorders. Morbidity onset may occur earlier in the adult lifespan for those with vs. without SMA. Whitney et al 2023 performed a cohort study using Medicare claims data from 2008 to 2016 to assess the comorbidities in adults with SMA (N=2,427) without treatment and compared them with 484,528 matched adults without SMA. The authors reported 30 comorbidities that are higher in SMA patients. In the study, the most common morbidities that were present in at least 25% of females with SMA were hypertension, chronic pulmonary disease, bone fragility, osteoarthritis, anemia, cardiac arrhythmias, fluid/electrolyte disorders, diabetes, and hypothyroidism. For males with SMA, it was hypertension, cardiac arrhythmias, diabetes, fluid/electrolyte disorders, chronic pulmonary disease, anemia, and osteoarthritis. The adjusted OR suggests that the morbidities in at least 25% of adults with SMA were 1.61 (hypothyroidism) to 7.80 (fluid/electrolyte disorders) compared to matched adults without SMA. The OR was highest for the ages 18-40 years of age, declined in the age group 40 to <75 and remained higher in adults older than age 75. The limitations of this study are that evidence of morbidities were limited to diagnostic claims and information on SMA type and symptoms, or onset were not available.

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 IV dose in young or neonatal patients and as a single IT dose in patients 2 years of age or older, respectively, the toxicology program consisted of single-dose toxicity, tolerability, and investigative studies in neonatal mice and juvenile or neonatal nonhuman primates and standard fertility and early embryonic development (FEED) and embryo-fetal development (EFD) studies in mice.

The animal species were chosen because of their established relevance as experimental toxicology species and their permissiveness to AAV9 transduction.

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 IV toxicity pivotal studies in neonatal mice (CRL 20122446 and COV 8384031) tested doses ranging from 7.9×10^{13} to 3.9×10^{14} vg/kg. Dose and test-article related mortality in mice was observed at doses ≥ 2.4×10^{14} 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 IV 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 ≥ 2.4×10^{14} vg/kg. When present in unscheduled sacrifice animals, atrial thrombi were typically ascribed as the cause of death.	**Zolgensma** 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 Zolgensma. 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 Zolgensma and none were considered clinically significant by the Investigators. 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 cardiac adverse event, involving troponin I,

Key Safety findings (from non-clinical studies)	Relevance to human usage
On this basis, the Maximum Tolerated Dose was defined as 1.5×10^{14} vg/kg, providing a safety margin of approximately 1.4 fold relative to the recommended clinical IV dose of 1.1×10^{14}vg/kg. IT administration of onasemnogene abeparvovec at 3×10^{13} vg/animal in primates led to findings in only one animal of mixed cell infiltrate and minimal hemorrhage of the right atrium. However, in situ hybridization of heart tissue from this animal did not support a direct role for onasemnogene abeparvovec in the observed microscopic findings.	Troponin T or unspecified troponin increased. Elevated troponin was not associated with any signs or symptoms indicative of cardiac tissue damage or decompensation. In the five years since the initial approval of Zolgensma, troponin I monitoring has been indicated at baseline prior to infusion, weekly for the first month, then biweekly for months two and three after infusion. A comprehensive review of the data showed that monitoring of troponin I in patients treated with Zolgensma was not indicative cardiac disorders, while increasing the burden of monitoring for the patients. Troponin I monitoring has been revised to obtain troponin I levels before the infusion and monitored as indicated based on the clinical evaluation. 'Cardiac adverse events' is considered an important potential risk for Zolgensma. **Itvisma** In the COAV101B12301 study, increased troponin I values have been observed in five (6.7%) patients in the Itvisma arm and two (3.9%) patients in the Sham arm, none of which were reported with cardiac findings. The highest increase from baseline recorded was up to 0.7399 ug/L, which was not considered to be clinically meaningful. The increased values in Itvisma patients were noted at various time points during the study and included week 1, week 4, week 10, and week 24 (two patients). Increases noted in Sham arm were observed at week 1 and week 24. All increased troponin I values returned to normal range at the end of study. No trend or pattern in increases in troponin I values have been observed in the study. No clinically significant changes to the troponin I levels have been reported in the patients in COAV101B12302 and AVXS-101-CL-102 studies. No cardiac adverse events have been reported in the COAV101B12301 and COAV101B12302 studies. Review of blood pressure and pulse rates in the subjects exposed to Itvisma in clinical trials, did not identify any trend or pattern. Based on clinical data the non-clinical findings are not expected to translate to humans, hence "cardiac adverse events" has not been carried forward as a risk for Itvisma.
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 7.9×10^{13} vg/kg in mice.	**Zolgensma** 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. In a post-authorization study COAV101A12306 including 24 children weighing ≥8.5 kg to ≤21 kg (aged approximately 1.5 to 9 years; 21 discontinued previous SMA treatment) increased transaminases were observed in 23 out of 24 patients. The patients were asymptomatic and there were no elevations of bilirubin. The AST and ALT elevations were managed with the use of corticosteroids, typically with prolonged duration (at Week 26, 17 patients were continuing prednisolone, at Week 52, 6 patients were still receiving prednisolone) and/or a higher dose.

Key Safety findings (from non-clinical studies)	Relevance to human usage
In cynomolgus monkeys, onasemnogene abeparvovec-related liver findings were observed after IT and IV administration at doses of ≥ 3×10^{13} vg/animal and 1.1×10^{14} 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 IT administration, and oval cell hyperplasia after IV administration. These findings correlated with transient, increased aminotransferase activity (alanine and aspartate) at doses of onasemnogene abeparvovec ≥ 3×10^{13} vg/animal following IT administration or 1.1×10^{14} vg/kg following IV administration. After long-term observation (12- and 6-months) following IT and IV administration, respectively, these liver findings (single cell necrosis of hepatocytes and oval cell hyperplasia), demonstrated partial (IV) or complete (IT) reversibility.	**Itvisma** In the 52-week pooled analysis, hepatic enzyme increased were reported in 9.4% of patients. Most of these events occurred within the first 3 months after treatment. 4.7% had ALT or AST >3xULN. The elevations were transient and resolved in all patients. The majority of patients received the recommended dose and duration of prednisolone. Hepatotoxicity is an important identified risk.
Dorsal root ganglia In cynomolgus monkeys, IT and IV 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 IT administration. Axonal degeneration and related findings in the spinal cord, spinal nerve roots and peripheral nerves were considered secondary to neuronal degeneration in the DRG.	The etiology of microscopic findings of DRG inflammation is complex and not well understood (Hordeaux et al 2020). In humans, inflammatory mediated injury to the DRG leads to simultaneous degeneration of short and long axons resulting in multimodal sensory deficits that do not exhibit length dependency. This clinical entity is referred to as a sensory ganglionopathy or sensory neuronopathy. Typically, patients exhibit severe loss of joint position and vibration sense, which may clinically manifest as limb and gait ataxia, pseudoathetosis, and diminished deep tendon reflexes. Both positive (tingling, burning, pain) and negative (numbness or loss of sensation) sensory phenomena have been described, often in a patchy, asymmetrical distribution. Paraesthesias are less common. More proximal sites, including the face and tongue, may also be involved. The patchy distribution of symptoms associated with ganglionopathy (caused by the simultaneous damage to short and long length axons) contrast the typical length dependent degeneration characteristic of many sensory neuropathies caused by inherited conditions, metabolic deficiencies, toxins, autoimmune disease, or infection. Distribution alone, however, is not pathognomonic as mononeuritis multiplex may also present with deficits in a patchy distribution and determination of the underlying etiology and mechanism of injury is necessary for definitive diagnosis (Sheikh and Amato 2010). Two published studies based on nerve conduction measurements, show that the sensory neurons are affected by the pathological processes in SMA patients. Shorrock et al (2019) emphasize the significant role of sensory neurons in the pathogenesis of SMA. Defects in sensory neurons include abnormal sensory conduction, loss of sensory nerve fibers, and reduced synaptic inputs to motor neurons. The authors indicated that sensory neuron dysfunction

Key Safety findings (from non-clinical studies)	Relevance to human usage
After 6- and 12-months of observation following IV and IT 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 IV administration of onasemnogene abeparvovec at 1.1×10^{14} 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. • At 12 months following IT administration, onasemnogene abeparvovec 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 ≥ 1.2×10^{13} 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 1.2×10^{13} 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 IV or IT administration to cynomolgus monkeys, similar findings	contributes to motor neuron degeneration and death. Pro et al (2021) investigated the progression of sensory neuropathy in 28 SMA type 1 patients of different ages, compared to 93 healthy subjects. The findings reveal that SNAP amplitudes decrease with increasing age in both the sural and median nerves, indicating that sensory neuropathy in SMA type 1 is age dependent. Younger patients exhibit normal SNAP amplitudes, while older patients show signs of axonal neuropathy. **Zolgensma** No reported AEs were suggestive of DRG toxicity. No histological evidence was identified to confirm DRG toxicity from the available information after meaningful duration of exposure to Zolgensma [PSUR; Reporting interval: 24-May-2023 to 23-May-2024]. A multicenter pilot study (Matesanz et al 2024) compared the efficacy of preemptive therapy using either onasemnogene abeparvovec alone (monotherapy) or onasemnogene abeparvovec in combination with an SMN2 augmenting agent (dual therapy) administered within six postnatal weeks to “presymptomatic” children at risk for infantile-onset SMA (two copies of SMN2), separated into appropriately matched parallel cohorts. The secondary aim was to evaluate muscle ultrasound to track the corresponding tissue response. As DRG toxicity related to AAV9-mediated SMN gene replacement is based on preclinical studies in mice, piglets, and NHPs and the relevance of these findings to humans is unknown, this study incorporated sensory nerve conduction studies as a measure of intravenous onasemnogene abeparvovec safety, to collect pertinent human data. Among 23 children enrolled in the study, 11 (two SMN2 copies treated with onasemnogene abeparvovec plus SMN2 augmentation by risdiplam or nusinersen (n=7); two SMN2 copies treated with onasemnogene abeparvovec only (n=3); and three SMN2 copies treated with onasemnogene abeparvovec only (n=1)) had sensory testing of the sural nerve along a median distance of 6.5 cm (range: 4.5–10) at median postnatal age 2.3 months (range: 0.6–42). Although the numbers were limited, no apparent differences in sensory nerve action potential (SNAP) properties between the three treatment groups were observed and all 11 children who completed sensory testing achieved a minimal sural nerve amplitude ≥6 µV, within the normal reference range for age. **Itvisma** In Study B12301 Period 1, there were 3 participants with treatment-emergent AEs reported under the AESI signs and symptoms that may be suggestive of DRG toxicity: 2 participants (2.7%) in the Itvisma arm, and 1 participant (2.0%) in the Sham arm [Study B12301 52w-Section 12.3.3]. • The first case in the Itvisma arm is a [redacted] participant who experienced “numbness in both legs” (hypoesthesia) approximately 3 weeks post-dose, which evolved to paresthesia and associated discomfort primarily affecting the feet. Throughout the course of symptoms multiple treatments were administered, including gabapentin, tricyclic antidepressants (nortriptyline and amitryptiline), pregabalin, IVIG, methylprednisolone, rituximab, and clemastine. The effect of treatment on the course of

Key Safety findings (from non-clinical studies)	Relevance to human usage
have been reported after administration of AAV9 vectors in rhesus macaques and mini-pigs (Hinderer et al 2018, Hordeaux et al 2018).	symptoms remains unclear, though symptomatic improvement with nortriptyline was reported. At Week 52, this participant discontinued the study due to ineligibility for Period 2. • The second case in the Itvisma arm is [redacted] participant who experienced "tingling sensation over both feet" (paresthesia) at 17 days post-dose. At Week 52, symptoms were stable. Throughout the course of symptoms multiple treatments were administered, including methylprednisolone IV, gabapentin, omeprazole, furosemide, TENS, and IVIG. After washout from IVIG, this participant entered Period 2. In both participants, nerve conduction studies revealed decreasing SNAP amplitudes, with relative preservation of conduction velocities, in distributions correlating with sensory symptoms. In parallel, the size of affected areas remained subjectively stable or diminished. Taken together, these findings suggested a monophasic, sensory axonopathy or sensory ganglionopathy. Interestingly, diminished vibration sense and proprioception were not observed, though nerve conduction study results confirmed large fiber involvement. A key feature differentiating sensory neuropathy from the sensory ganglionopathy is the distribution of symptoms. Sensory, axonal neuropathies are typically length dependent: symptoms progress from distal to proximal along the extremities. In contrast, sensory ganglionopathies typically present with sensory symptoms in a patchy distribution involving the extremities and trunk. However, given the limited distribution of symptoms in both cases, it was not possible to discern whether symptoms exhibit a length dependency. The case in the Sham arm involved a [redacted] participant who experienced mild, transient paraesthesia starting approximately 5 months after dosing, and resolved with no symptomatic treatments required. In the 52-week pooled safety analysis, signs and symptoms that may be suggestive of DRG toxicity AESI were reported in 4 participants (3.1%). Two of these participants were in the Itvisma arm of Study B12301, and these cases are described above. The other two participants were in Study B12302: one was a case of paraesthesia in feet in [redacted] reported within 28 days post dosing and resolved after 63 days, and a case of sensory disturbance on bilateral forearms, neck, and scalp in a [redacted] reported within 38 days post dosing and resolved within 3 days. The events were not serious and resolved without any treatment in both participants [OAV101B SCS-Section 2.7.5]. In the long-term safety analysis, no AESI of signs and symptoms that may be suggestive of DRG toxicity were reported from the end of the Week 52 period and until data cut-off date of the long-term studies LT-002 and A12308 [SCS Appendix-Table 2-2.7.2.2]. DRG toxicity is an important potential risk.
Repeat-dose toxicity	
No repeat-dose toxicity studies were performed with onasemnogene abeparvovec as onasemnogene	Not applicable

Key Safety findings (from non-clinical studies)	Relevance to human usage
abeparvovec is only intended for single dose administration.	
Reproductive/developmental toxicity In long term toxicology studies for both IV and IT, male or female reproductive organs have been assessed by careful standard histopathological examination of the ovaries, testes, and accessory reproductive organs up to 12-months duration in mice and juvenile cynomolgus monkeys. No treatment-related effects were observed. In mice fertility and early embryonic development (FEED) studies, onasemnogene abeparvovec did not impact fertility, fecundity, or mating indices; uterine examination data; or early embryonic development in male and female mice at doses of 1.1×10^{13} vg/kg or 1.1×10^{14} vg/kg administered intravenously. In a mice EFD study, onasemnogene abeparvovec was not detected in fetal tissues, and had no effect on cesarean section parameters, gravid uterine weight, corrected maternal body weight/body weight gain, covariate adjusted fetal body weight, or fetal external, visceral, or skeletal examinations at doses of 1.1×10^{13} vg/kg or 1.1×10^{14} vg/kg administered intravenously at gestation day 6. The no observed adverse effect level (NOAEL) for maternal and developmental toxicity is $1.1x10^{14}$ vg/kg, the highest dose level evaluated.	Onasemnogene abeparvovec is a recombinant adeno-associated virus (rAAV9), with all wild-type AAV coding DNA (including site-specific integration feature) removed from the capsid and replaced with DNA (human SMN gene) needed to produce the SMN protein. These alterations make the vector replication-deficient and vector DNA exist as an episome in transduced cells with no targeted integration into the host genome. Consequently, the possibility of incorporation of onasemnogene abeparvovec into the patient's chromosomal DNA is thought to be significantly reduced. NHP molecular localization data indicates scAAV9 germline transduction occurs in ovulating female but not male cynomolgus monkeys after IT or IV scAAV9 administration. Therefore, there remains a theoretical risk that scAAV9 could transduce the germline cells and specifically the oocytes of female recipients. Given that there is low risk for rAAVs to modify the germline DNA and be passed on to the following generation (Jakob et al 2005; Schuettrumpf et al 2006, Paneda et al 2009, Ferla et al 2017, Watanabe et al 2017, Watanabe et al 2018, Kanatsu-Shinohara et al 2022), the risk of vertical transmission for onasemnogene abeparvovec cannot be excluded with certainty. This nonclinical data indicates that onasemnogene abeparvovec at clinically relevant doses showed no embryo-fetal toxicity or teratogenicity and poses no increased risk for fertility and fetal abnormalities in this mouse model. Despite the limitations inherent in extrapolating findings directly to human biology, mice have consistently served as the standard model for developmental and reproductive toxicity studies and their use is broadly supported by regulatory authorities for such assessments. Together, these developmental toxicity studies suggest a highly favorable safety profile for onasemnogene abeparvovec with respect to reproductive and developmental toxicity at clinically relevant doses [Nonclinical Overview].
Genotoxicity and carcinogenicity No genotoxicity and carcinogenicity studies were performed with onasemnogene abeparvovec as these studies are generally not required for gene therapy vectors.	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 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 IV injection of rAAV9 expressing the mouse Hexb cDNA

Key Safety findings (from non-clinical studies)	Relevance to human usage
	(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 tumorigenic 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 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; Protocol Number: COAV101A12308, Version 4.0, 01-Aug-2024). There were 2 reports of tumors in patients treated with Zolgensma IV in the post-marketing setting. One report involves an epithelioid neoplasm of the spinal cord in a child with SMA treated with Zolgensma. The integration site analysis (ISA) was inconclusive due to the limited volume of neoplastic tissue available for analysis, however the overall causality assessment considering the expected integration frequency concluded that the tumor was not caused by the treatment (Retson L et al 2023). The second report concerns a low-grade astrocytoma reported in an infant male patient. Holzwarth D et al (2025) and discusses the integration investigations related to this case. The investigation concluded that the tumor was most likely preexisting before Zolgensma treatment, and that the treatment did not contribute to the initiation of the tumor.
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 [redacted]. 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 19-Feb-2025, 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]. The search has retrieved one case in post-marketing setting describing

Key Safety findings (from non-clinical studies)	Relevance to human usage
	an event of skin necrosis attributed to the underlying SMA. similar events were reported for onasemnogene abeparvovec. One alternative explanation for the ear lobe necrosis seen in onasemnogene abeparvovec study CL-302 patient [redacted] 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 [redacted] these procedures are quite common in persons treated in intensive care units. The ear lobe necrosis observed in patient [redacted] 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 age 7. 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. 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. There were no events of skin or ear lobe necrosis in the Itvisma program.
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

Key Safety findings (from non-clinical studies)	Relevance to human usage
	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. In Itvisma studies, the baseline serum anti-AAV9 antibody titers were below 1:50 in all Itvisma treated patients. Increases from baseline in anti-AAV9 antibody titers were observed in all Itvisma treated patients and remained elevated at 12 months following Itvisma administration with median titers ≥1:819200 in Phase III studies. The baseline CSF anti-AAV9 antibodies were negative for all patients. There was no clear association of post-dose serum anti-AAV9 titers with safety [OAV101B SCP-Section 5.4].

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 (applicable for Zolgensma only) 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

4.1.1 Zolgensma

Zolgensma has been administered intravenously in 4 Novartis-sponsored clinical studies, in which a total of 97 patients have been exposed to the drug. [redacted]

Study AVXS-101-CL-101 (Study CL-101) is a Phase 1, open-label, single-infusion, ascending-dose, single center study designed to evaluate safety and efficacy of Zolgensma gene transfer in SMA Type 1 patients genetically tested to confirm no functional copies of SMN1, and 2 copies of SMN2. It began in Apr-2014 in the US and completed enrolment of 15 patients in Dec-2015. Three patients were dosed in Cohort 1 (Dose: 3.7×10^{13} vg/kg IV) and 12 in Cohort 2 (Dose: 1.1×10^{14} vg/kg IV). The Cohort 2 dose was defined as the therapeutic dose (1.1×10^{14} vg/kg IV) used in all subsequent IV studies. All patients were dosed at 6 months or less, except one patient who was dosed beyond 6 months of age. 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).

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 1.1×10^{14} vg/kg of Zolgensma. Study enrolment was completed with 22 patients. All treated patients received the full dose of Zolgensma 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.

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 1.1×10^{14} vg/kg Zolgensma administered via IV infusion. Enrolment was closed on 08-Nov-2019.

AVXS-101-CL-302 (Study CL-302) is a completed, Phase 3, open-label, single-arm study of a single, one-time dose of 1.1×10^{14} vg/kg Zolgensma administered via IV infusion conducted in patients with SMA Type 1. Enrollment was closed on 21-May-2019.

The exposure data analysis presented in Tables 4-1, Tables 4-2 and Tables 4-3 is based on pooled data including all patients (N=97) who received the Zolgensma 1.1×10^{14} vg/kg IV dose in Study CL-101, Study CL-302, Study CL-303, Study CL-304. These summaries are based on completed studies with latest data cut-off dates (CL-101: 26-Dec-2017; CL-302: 16-Nov-2020; CL-303: 12-Dec-2019; CL-304: 15-Jul-2021).The first-in-human clinical trial of Zolgensma 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 Zolgensma 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 Zolgensma 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 1.1×10^{14} vg/kg. The Cohort 2 dose is the proposed therapeutic dose. The therapeutic i.v. dose of Zolgensma used in all other studies is determined by the ddPCR assay and is 1.1×10^{14} 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).

Intravenous administration exposure is presented in Table 4-1.

Table 4-1 Follow up time since Zolgensma dosing

Duration	AVXS-101-CL-101 N=12 n (%)	AVXS-101-CL-302 N=33 n (%)	AVXS-101-CL-303 N=22 n (%)	AVXS-101-CL-304 N=30 n (%)	Overall N=97 n (%)
Time Since Dosing (Months)					
n	12	33	22	30	97
Mean	24.5	14.8	14.0	21.1	17.8
StdDev	0.53	3.12	2.95	3.17	4.85
Median	24.4	14.7	14.8	22.9	17.1
Minimum	23.8	1.8	5.7	17.4	1.8
Maximum	25.7	21.1	18.1	25.6	25.7
Categories for Time Since Dosing (Months)					
0-<3 mos	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.0)
3-<6 mos	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.0)
6-<9 mos	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.0)
9-<12 mos	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12-<24 mos	1 (8.3)	32 (97.0)	20 (90.9)	24 (80.0)	77 (79.4)
24-<36 mos	11 (91.7)	0 (0.0)	0 (0.0)	6 (20.0)	17 (17.5)
36-<48 mos	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 48 mos	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 4-2 Follow up time since Zolgensma dosing by gender

Duration	AVXS-101-CL-101 N=12 n (%)		AVXS-101-CL-302 N=33 n (%)		AVXS-101-CL-303 N=22 n (%)		AVXS-101-CL-304 N=30 n (%)		Overall N=97	
Sex	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)
Total	12 (100.0)	294.2	33 (100.0)	490.0	22 (100.0)	307.0	30 (100.0)	631.7	97 (100.0)	1722.9
Female	7 (58.3)	171.9	19 (57.6)	284.9	12 (54.5)	160.8	19 (63.3)	396.2	57 (58.8)	1013.9
Male	5 (41.7)	122.3	14 (42.4)	205.1	10 (45.5)	146.2	11 (36.7)	235.5	40 (41.2)	709.0

Table 4-3 Follow-up time since Zolgensma dosing by race

Duration	AVXS-101-CL-101 N=12 n (%)		AVXS-101-CL-302 N=33 n (%)		AVXS-101-CL-303 N=22 n (%)		AVXS-101-CL-304 N=30 n (%)		Overall N=97	
Sex	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)	Subjects n (%)	Time since dosing (Months)
Total	12 (100.0)	294.2	33 (100.0)	490.0	22 (100.0)	307.0	30 (100.0)	631.7	97 (100.0)	1722.9
White	11 (91.7)	270.4	0	-	11 (50.0)	148.0	18 (60.0)	389.2	40 (41.2)	807.7
Black Or African American	0	-	0	-	3 (13.6)	43.9	1 (3.3)	17.9	4 (4.1)	61.8
American Indian Or Alaska Native	0	-	0	-	0	-	1 (3.3)	22.9	1 (1.0)	22.9
Asian	0	-	0	-	2 (9.1)	29.8	4 (13.3)	82.9	6 (6.2)	112.7
Other	1 (8.3)	23.8	0	-	6 (27.3)	85.3	6 (20.0)	118.7	13 (13.4)	227.8
Unknown	0	-	33 (100.0)	490.0	0	-	0	-	33 (34.0)	490.0

4.1.2 Itvisma

Study OAV101B12301 (hereafter referred to as B12301) is a pivotal Phase III, randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of Itvisma in patients with SMA who were 2 to <18 years of age, had onset of clinical symptoms at ≥6 months of age, were treatment naïve, sitting, and never walked independently. In Period 1, patients were randomized to receive 1.2×10^{14} vg dose Itvisma or Sham procedure on Day 1 and were followed for 52 weeks (Period 1). Eligible patients subsequently entered Period 2, where patients who received a sham procedure in Period 1 received Itvisma and patients who received Itvisma in Period 1 received sham procedure on the Week 52 +1 Day visit. Patients in Period 2 were followed for 12 weeks, for a total duration of 64 weeks.

Study OAV101B12302 (hereafter referred to as B12302) is a Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety and tolerability of Itvisma in patients 2 to <18 years of age with SMA who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). All patients received 1.2×10^{14} vg Itvisma and were followed for 52 weeks.

Study AVXS-101-CL-102 (Study CL-102) is a Phase I/II, open-label, dose ranging study of Itvisma conducted in sitting but non-ambulatory patients with SMA and bi-allelic deletion of SMN1 and 3 copies of the survival motor neuron 2 gene (SMN2) who were at least 6 months and up to 60 months of age at time of dosing. The study consisted of 2 age groups: 6 to <24 months of age, and 24 to <60 months of age. This study evaluated three different doses of Itvisma in consecutive dose cohorts of patients: Cohort 1 (Dose A: 6.0×10^{13} vg), Cohort 2 (Dose B: 1.2×10^{14} vg), and Cohort 3 (Dose C: 2.4×10^{14} vg).

The safety analysis (52 week pooled analysis) is based on pooled data including all patients (N=127) who received the Itvisma 1.2×10^{14} vg dose in Study B12301 (Period 1), Study CL-102 and or Study B12302, providing data with up to 52 weeks of follow-up in treatment naïve patients age 2 to <18 years, treatment naïve patients age 6 to <60 months and treatment experienced aged 2 to <18 years, respectively.

The Pooled Safety Analysis Set included a total of 178 participants, of whom 167 participants had received Itvisma at a dose of 1.2×10^{14} vg: 115 had received Itvisma in Study B12301 (75 in Period 1, 40 in Period 2), 27 had received Itvisma in Study B12302, and 25 had received Itvisma in Study CL-102. Eleven participants had received Sham only (they received Sham in Period 1 but had not entered Period 2 to receive Itvisma). At the time of analysis, Study B12301 Period 2 was ongoing (Table 4-4 and Table 4-5).

Table 4-4 Follow-up time since Itvisma dosing and age at data cut-off by gender and overall (Pooled Safety Analysis Set)

	Female N=88 n (%)	Male N=90 n (%)	Overall N=178 n (%)
Follow-up time since OAV101B dosing (months)[1]			
N	85	88	173
Mean (SD)	17.05 (14.180)	15.21 (14.451)	16.11 (14.307)
Median	14.72	14.57	14.69
Q1 - Q3	11.76 - 18.69	5.96 - 16.76	11.30 - 17.54
Min – Max	2.7 - 74.5	2.6 - 71.0	2.6 - 74.5
Follow-up time since OAV101B dosing (years)[1]			
N	85	88	173
Mean (SD)	1.42 (1.182)	1.27 (1.204)	1.34 (1.192)
Median	1.23	1.21	1.22
Q1 - Q3	0.98 - 1.56	0.50 - 1.40	0.94 - 1.46
Min - Max	0.2 - 6.2	0.2 - 5.9	0.2 - 6.2
Less than 1 year - n (%)	26 (29.5)	36 (40.0)	62 (34.8)
At least 1 year and less than 3 years - n (%)	53 (60.2)	47 (52.2)	100 (56.2)
At least 3 years - n (%)	6 (6.8)	5 (5.6)	11 (6.2)
Sum of follow-up time (years)[2]	120.7	111.5	232.3
Age (years) at data cut-off date[3]			
n	88	90	178
Mean (SD)	6.98 (3.246)	7.42 (3.498)	7.20 (3.374)
Median	6.30	6.50	6.36
Q1 - Q3	4.70 - 8.32	4.87 - 9.32	4.79 - 8.56
Min - Max	2.9 - 18.2	2.0 - 18.7	2.0 - 18.7

The pooled safety analysis set (PSAF) is comprised of all patients who were enrolled in any of the studies and received OAV101B 1.2×10^{14} vg or a sham IT administration.

[1] Follow-up time since OAV101B dosing (days) = [Min(Date of death, Date of discontinuation from study, Cut-off date, Date of Completion) – Date of treatment in parent study + 1].

Follow-up time since OAV101B dosing (months) = Follow-up time since OAV101B dosing (days) / 30.4375.

Follow-up time since OAV101B dosing (years) = Follow-up time since OAV101B dosing (days) / 365.25.

[2] Sum of follow-up time per patient across all patients.

[3] Age (years) at data cut-off date = [Min(Date of death, Date of discontinuation from study, Cut-off date, Date of Completion) – Date of Screening visit 1 + 1]/365.25 + Age (years) at screening visit 1 from parent study.

Cut off dates used: COAV101A12102 (01-Dec-2021), COAV101B12301 (27-May-2025), COAV101B12302 (21-Dec-2024), AVXS-101-LT-002 (24-Jun-2024), COAV101A12308 (05-Nov-2024).

Source: [OAV101B SCS Appendix 1-Table 1-6.a]

Table 4-5 Follow-up time since Itvisma dosing and age at data cut-off by race and overall (Pooled Safety Analysis Set)

	White N=45 n (%)	Black or African American N=9 n (%)	Asian N=85 n (%)	Other N=10 n (%)	Unknown N=29 n (%)	Overall N=178 n (%)
Follow-up time since OAV101B dosing (months)[1]						
n	44	9	84	9	27	173
Mean (SD)	22.46 (21.576)	10.02 (6.875)	13.86 (8.694)	17.99 (23.583)	14.17 (7.393)	16.11 (14.307)
Median	12.99	14.95	14.75	11.79	14.98	14.69
Q1 - Q3	11.79 - 19.89	2.79 - 15.67	11.55 - 16.84	2.99 - 14.75	7.59 - 20.27	11.30 - 17.54
Min - Max	2.8 - 71.0	2.8 - 16.8	2.7 - 69.4	2.6 - 74.5	2.8 - 26.9	2.6 - 74.5
Follow-up time since OAV101B dosing (years)[1]						
n	44	9	84	9	27	173
Mean (SD)	1.87 (1.798)	0.84 (0.573)	1.16 (0.724)	1.50 (1.965)	1.18 (0.616)	1.34 (1.192)
Median	1.08	1.25	1.23	0.98	1.25	1.22
Q1 - Q3	0.98 - 1.66	0.23 - 1.31	0.96 - 1.40	0.25 - 1.23	0.63 - 1.69	0.94 - 1.46
Min - Max	0.2 - 5.9	0.2 - 1.4	0.2 - 5.8	0.2 - 6.2	0.2 - 2.2	0.2 - 6.2
Less than 1 year - n (%)	17 (37.8)	4 (44.4)	26 (30.6)	5 (50.0)	10 (34.5)	62 (34.8)
At least 1 year and less than 3 years - n (%)	18 (40.0)	5 (55.6)	57 (67.1)	3 (30.0)	17 (58.6)	100 (56.2)
At least 3 years - n (%)	9 (20.0)	0	1 (1.2)	1 (10.0)	0	11 (6.2)
Sum of follow-up time (years)[2]	82.4	7.5	97.0	13.5	31.9	232.3
Age (years) at data cut-off date[3]						
n	45	9	85	10	29	178
Mean (SD)	7.95 (4.281)	7.70 (3.485)	7.06 (3.360)	6.64 (1.489)	6.51 (1.860)	7.20 (3.374)
Median	6.57	7.08	6.06	6.34	6.29	6.36
Q1 - Q3	5.13 - 9.62	5.60 - 9.22	4.46 - 8.59	5.49 - 7.41	5.18 - 8.08	4.79 - 8.56
Min - Max	2.0 - 18.7	4.4 - 15.6	3.1 - 18.2	4.5 - 9.6	3.5 - 10.2	2.0 - 18.7

	White N=45 n (%)	Black or African American N=9 n (%)	Asian N=85 n (%)	Other N=10 n (%)	Unknown N=29 n (%)	Overall N=178 n (%)

The pooled safety analysis set (PSAF) is comprised of all patients who were enrolled in any of the studies and received OAV101B 1.2×10^{14} vg or a sham IT administration.

[1] Follow-up time since OAV101B dosing (days) = [Min(Date of death, Date of discontinuation from study, Cut-off date, Date of Completion) – Date of treatment in parent study + 1].

Follow-up time since OAV101B dosing (months) = Follow-up time since OAV101B dosing (days) / 30.4375.

Follow-up time since OAV101B dosing (years) = Follow-up time since OAV101B dosing (days) / 365.25.

[2] Sum of follow-up time per patient across all patients.

[3] Age (years) at data cut-off date = [Min(Date of death, Date of discontinuation from study, Cut-off date, Date of Completion) – Date of Screening visit 1 + 1]/365.25 + Age (years) at screening visit 1 from parent study.

Other includes all other and multiple races.

Cut off dates used: COAV101A12102 (01-Dec-2021), COAV101B12301 (27-May-2025), COAV101B12302 (21-Dec-2024), AVXS-101-LT-002 (24-Jun-2024), COAV101A12308 (05-Nov-2024).

Source: [OAV101B SCS Appendix 1-Table 1-6.b]

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 (applicable for Zolgensma and Itvisma)

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, IV 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 ligand 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. Patients should be tested for the presence of AAV9 antibodies before administration 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)* (applicable for Zolgensma only).	Excluded based on predicted less severe phenotype so that a comparison with the published natural history would be feasible.	No	This population of patients is not considered as missing information because: 1. Taking into account the rarity of patients with a single base substitution in

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			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

5.2.1 Zolgensma

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. These limitations have been largely overcome by more than 4000 patients exposed being in the post-marketing setting and the LTFU studies.

5.2.2 Itvisma

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. Rare and long-term safety is primarily informed by the post-marketing experience with Zolgensma and it is supported by data collected in LTFU; delayed safety issues have not been identified.

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	For Zolgensma: all patients were infants (age range of 0.3 to 7.9 months) For Itvisma: all patients were part of the pediatric population (0.6 - 17.7 years of age)
Pregnant women	
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Not included in the clinical development program
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	For Zolgensma: 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 bi-allelic 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. For Itvisma: COAV101B12301 included participants with diagnostic confirmation of 5q SMA, who were between the ages of 2 and <18 years of age. COAV101B12302 included participants with SMA with bi-allelic mutations in SMN1 gene, and any number of copies of SMN2 gene, aged 2 to < 18 years. AVXS-101-CL-102 included patients with bi-allelic SMN1 deletion and 3 copies of SMN2 without the genetic modifier, who were between the ages of 6 and <60 months.

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 from Zolgensma until 23-May-2025 is 4984 patients. Post-marketing data is only available for Zolgensma.

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

Table 6-1 Cumulative exposure from marketing experience

Formulation	EEA	[redacted]	[redacted]	ROW
Zolgensma	1529	[redacted]	[redacted]	1724

This table includes cumulative data obtained from 24-May-2019 to 23-May-2025

Source of data: [PSUR (reporting interval: 24-May-2024 to 23-May-2025)]

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 susceptible to misuse for illegal purposes.

7.2 Specific risks of advanced therapy medicinal products

7.2.1 Zolgensma

Zolgensma 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 -60ºC. 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 validated pre-conditioned [redacted] shipper container 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.

7.2.1.1 Shipping validation

Shipping Validation Performance Qualification was performed to confirm that the selected shipper for Zolgensma was able to protect the drug during shipping and assess shipping for climate variations. Zolgensma 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 validated pre-conditioned [redacted] shipper container to maintain shipment temperatures ≤ -60°C.

Three shipments were made with Zolgensma Drug Product and Zolgensma Drug Product Surrogate ([redacted]). The Zolgensma Drug Product Surrogate consisted of [redacted] filled into CZ vials at a volume of either 5.5 mL or 8.3 mL. The Zolgensma 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 Zolgensma Drug Product and Zolgensma 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 [redacted], which satisfied the requirement of greater than or equal to [redacted]. The duration of each shipment also met the requirement of being greater than or equal to [redacted]. 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 Zolgensma Drug Product and Zolgensma 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 validated pre-conditioned [redacted] shipper container 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.

7.2.1.1.1 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 Zolgensma 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 Zolgensma drug product (Table 7-1). The product stress studies concluded that the quality attributes evaluated remain stable through various temperature excursions.

[redacted]

7.2.2 Itvisma

Itvisma is manufactured in the US. Product is filled in vials with one fill volume of 3.0 mL. The product is stored at or below -60ºC. The vials are tested and labelled and shipped frozen to a commercial manufacturing organization in the EEA. The main risk associated with the logistics of the product is a break in the cold chain.

7.2.2.1 Shipping validation

Drug product is filled into 5 mL CZ vials to a nominal volume of 3.0 mL and frozen at ≤ -60°C. The commercial secondary packaging presentation consists of one labelled, filled vial per carton. Each carton holds one vial and package insert(s). Up to 16 cartons are placed in a plastic bag and shipped via a validated pre-conditioned [redacted] shipper container with a temperature monitoring device(s). For bulk configurations, 1 to 25 bulk labelled, filled vials are packed into a 5” × 5” × 2” bulk carton, placed in a plastic bag, and shipped in a validated pre-conditioned [redacted] shipper container. Bulk shipments consist of a maximum of 4 cartons packed into a validated pre-conditioned [redacted] shipper container for a maximum total of 100 vials per shipper.

The validated pre-conditioned [redacted] shipper container is packed with dry ice to maintain shipment temperatures ≤ -60°C.

The performance of the validated pre-conditioned [redacted] shipper container was tested against the ISTA 7D summer profile with temperature holding time as the evaluation criteria. This qualification demonstrated the validated pre-conditioned [redacted] shipper container can maintain product temperatures of ≤ -65°C or ≤ -60°C during shipping.

To evaluate the validated pre-conditioned [redacted] shipper container thermal performance when shipping product, a shipping validation performance qualification was executed using the worst-case product shipping configuration. Shippers were transported via multiple flights throughout the US and were subjected to multiple holds to achieve the worst-case routing distance and duration. Upon test completion, the validated pre-conditioned [redacted] shipper container demonstrated its ability maintain the product storage temperature of ≤ -60ºC when shipping the worst-case drug product thermal load and thus is considered acceptable for product shipment.

7.2.2.1.1 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 Itvisma material was stressed by performing the following challenges through laboratory studies. The results of this process showed no impact to the Itvisma drug product (Table 7-2). The product stress studies concluded that the quality attributes evaluated remain stable through various temperature excursions.

7.2.3 Flow-chart of the logistics of the therapy

Not applicable.

7.2.4 Risks to living donors (where applicable)

Not applicable.

7.2.5 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).

7.2.6 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).

7.2.7 Risks related to interaction of the product and the patient

Not applicable.

7.2.8 Risks related to scaffolds, matrices and biomaterials

Not applicable.

7.2.9 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).

7.2.10 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

This section is updated to reflect the current information available for Zolgensma and the addition of Itvisma in the integrated RMP.

8.1.1 Part II Module 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.

Potential medication errors due to single prescribing information and associated consequences

Zolgensma is administered one-time intravenously at a dose of 1.1×10^{14} vg/kg calculated based on a patient's body weight. The patient specific weight-based dosing is important to ensure sufficient systemic delivery of vector and ultimately expression of the SMN1 protein in the target motor neurons to achieve improved motor functions and lifesaving efficacy in the SMA population who would otherwise have a limited life expectancy.

Itvisma is administered one-time intrathecally at a dose of 1.2×10^{14} vg irrespective of patients age and weight. IT administration targets the central nervous system (CNS) thereby allowing for neuronal transduction and limiting the amount of systemic exposure. The viral vector load with IT delivery directly into the CNS requires about 10-fold less vector concentration compared to IV for effective distribution throughout the spinal cord as well as reduced viral vector distribution in major peripheral organs such as the liver, which should optimize the safety profile with IT delivery.

Misinterpretation of the route of administration could lead to administration of an erroneous dose of product.

- An IV vial administered via IT route could result in an increased risk of CNS and systemic toxicities due to high vector load delivered directly to the target tissue.
- An IT vial administered via IV route could result in a potential lack of efficacy given significantly lower vector load and inadequate distribution to the CNS target tissue.
- In both scenarios, due to the development of neutralizing antibodies to the vector, there would be no opportunity for re-dosing or re-treatment of the medicinal product which leads to a missed opportunity for improvement in motor function and quality of life for the patient.

The potential medication error is minimized by the creation of distinct trade names and stand-alone labels and will be followed up via routine pharmacovigilance.

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

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 Risks not considered important for inclusion in the list of safety concerns for Itvisma

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)
Infections and infestation: Very common: Upper respiratory tract infection
Nervous system disorders: Very common: Headache; Common: Dizziness
Gastrointestinal disorders: Very common: Vomiting
General disorders and administration site conditions: Very common: Pyrexia
AEs potentially associated with the lumbar puncture procedure: Headaches and dizziness have occurred with higher frequency in the Itvisma arm, with the difference being more pronounced within 72 hours following dosing. Based on the timing of these events and the known relationship with the lumbar puncture procedure, these could be related to the procedure. Itvisma is designed as a one-time treatment administered by trained professionals at specialized centers.
AEs associated with the procedure: General anesthesia and/or sedation are routinely performed in children to reduce procedure-related anxiety, pain, and distress, and to increase the overall success rate of lumbar puncture. Children with SMA who have moderate to severe muscle weakness and/or severe scoliosis are at higher risk for hypoventilation and respiratory compromise. Thus, if deep sedation or general anesthesia is used, assisted ventilation may be required by either non-invasive or invasive means (Hache et al 2016). Itvisma is designed as a one-time treatment administered by qualified professionals at specialized centers.

Table 8-3 ATMP-specific risks (applicable for Zolgensma and Itvisma)

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	Zolgensma: Zolgensma DNA can be found in the blood, urine, saliva, stool, and nasal secretion. Zolgensma shedding was primarily via stool. Peak shedding in most patients was observed within 7 days post-dose for stool, and within 2 days post-dose for saliva, urine and nasal secretion. The majority of the Zolgensma vector DNA was cleared within 30 days post-dose. The risks associated with the shed

Risk	Reason for not being an important risk
	vector are not known at this time; however, because the vector is nonpathogenic and cannot replicate, it is believed that shed vector is unlikely to result in clinically significant adverse effects. 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. Shedding is reported to be dependent on the dose and route of administration; the IV route can be considered a worst case scenario for AAV shedding. However, even in the case of shedding, the AAV vectors do not propagate to outside cells. 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. Itvisma: The Itvisma shedding profile in stool, saliva, urine, and nasal secretion was similar across the studies. Itvisma shedding was primarily via stool in all studies. Peak shedding in stool across studies was estimated to be between 0.0048% to 0.0297% of total dose. Peak shedding in most patients was observed within 10-, 3-, 2-, and 8 days post-dose for stool, saliva, urine and nasal secretion, respectively. Thereafter, median concentration of Itvisma DNA declined rapidly to BLQ or less than 10% of peak concentration in stool, urine, saliva and nasal secretion by 2-, 1-, 1- and 3-weeks post-dose, respectively. By 2 weeks post-dose, the majority of the Itvisma vector DNA (>90%) was cleared. The median concentration of Itvisma DNA in stool after 1 week post-dose was below what would be required for an in vitro transduction assay whereas the median concentration of Itvisma DNA in urine and saliva remained below the in vitro transduction assay threshold at all timepoints. Itvisma vector DNA was BLQ in most patients (75%) by 6 weeks, 1 weeks, 4 week and 10 weeks post-dose in stool, urine, saliva, and nasal secretion, respectively. However, the low levels of shedding during this period were below the threshold necessary for an in vitro transduction assay and can be practically considered as non-infectious. Peak Itvisma shedding in stool was ~70-fold lower than that of Zolgensma.
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 IV administration, AAV9 vectors (like onasemnogene abeparvovec) appear to distribute to the skeletal muscle, liver, lung and CNS

Risk	Reason for not being an important risk
	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.
Use in patients with anti AAV9 antibody titres > 1:50 and higher vector loads required (for Itvisma only)	Patients with anti-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. Itvisma will be administered as a one-time, single, bolus injection at the fixed-dose of 1.2×10^{14} vg. As the dose is not dependent on the weight of the patient, heavier patients will not be exposed to higher vector loads.

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

Table 8-4 Important identified risks (applicable for Zolgensma and Itvisma)

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Hepatotoxicity	AEs of elevated transaminases of which some were serious have been observed. Overall, the incidence and severity of these events was higher in patients with IV treatment than those with IT. In general, these elevations were not associated with clinical symptoms. 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 after Zolgensma administration. Decreases were clinically asymptomatic, transient and resolved during the observation period. The benefit of Zolgensma as an effective treatment for the debilitating and life-threatening

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	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. Transient decreases in platelet counts were typically observed within the first week after Itvisma administration. In most cases, platelet counts were >75×10^9/L and platelet counts returned to baseline two weeks following Itvisma injection. Decreases were clinically asymptomatic, transient and resolved during the observation period. The benefit of Itvisma 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 or until platelet counts return to baseline.
Thrombotic microangiopathy	Thrombotic microangiopathy (TMA) was initially not observed in Zolgensma clinical trials but in the post-marketing setting of Zolgensma. No cases of TMA have been observed in the Itvisma 52-week pooled safety analysis. TMA is a life-threatening condition characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. As thrombocytopenia is a key feature of TMA, platelet counts should be monitored on a regular basis following Itvisma injection, as well as signs and symptoms of TMA, such as hypertension, bruising easily, seizures, or decreased urine output. Should clinical signs, symptoms and/or laboratory findings consistent with TMA occur, prompt action needs to be taken. Considering the severity and seriousness of these events coupled with the need for early detection and urgent intervention, TMA is considered an important identified risk for Zolgensma and Itvisma.

Table 8-5 Important potential risks (applicable for Zolgensma and Itvisma)

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Cardiac adverse events (applicable for Zolgensma only)	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 Zolgensma. Cases of tachycardia and bradycardia occurred in the clinical trials with Zolgensma; however, the significance was not determined. Minor transient increases in CK- MB and troponin I were reported with no associated clinical sequelae. In the Itvisma 52-week pooled analysis, one patient (0.8%) had an increase blood creatinine phosphokinase myocardial band (CPK-MB), this event was mild in severity and was considered related to the study treatment. The outcome of the event was reported as resolved. There have been no significant changes to the troponin I levels in the 52-week pooled analysis. The benefit of Zolgensma 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.

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required (applicable for Zolgensma only)	Patients with anti-AAV9 titres > 1:50 were excluded from clinical studies thus, the safety of Zolgensma in this population is unknown. Increases in anti-AAV9 titres were observed after the administration of Zolgensma during clinical studies. This response was expected. However, there were no apparent relationships between anti-AAV9 titre and safety or efficacy.
Dorsal root ganglia toxicity/peripheral sensory neuropathy	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 Itvisma 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. Peripheral sensory neuropathies have been reported in 2 patients in B12301 study however the non-clinical findings of DRG inflammation have not been confirmed in patients from clinical trials or post-marketing experience.
Tumorigenicity due to chromosomal integration	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. Two reports of malignancies were reported in patients with Zolgensma in the post-marketing setting. Integration site analyses did not support treatment contribution to the initiation of the tumor.

Table 8-6 Missing information (applicable for Zolgensma and Itvisma)

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only)	The long-term efficacy and safety of Zolgensma therapy in light of adverse events that are rare or have long latency, cannot be defined based on available evidence. As of 01-Jul-2024, 13 of the 15 subjects (86.7%) who completed Study CL 101 were enrolled in the LTFU study (Study LT-001). As of 01-Jul-2024, the patients in Study LT-001 have been followed for up to 103.92 months with observation ongoing. The long-term effect of Zolgensma therapy is considered missing information and will be monitored to ensure that the risk-benefit balance of the product is maintained.
Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)	The long-term safety of Itvisma therapy in light of adverse events that are rare or have long latency, cannot be defined based on available evidence. As of 24-Jun-2024, the participants treated in study CL-102 have been followed up in Study LT-002 for up to 63.82 months (min-max: 34.8- 76.4 months) with observation ongoing (Study LT-002). In addition, the patients treated in Phase 3 studies (COAV101B12301 and COAV101B12302),

Missing information	Risk-benefit impact (Reasons for classification as missing information)
	who consent for long-term follow up, are being further monitored in study COAV101A12308.
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 (applicable for Zolgensma only)	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 Zolgensma 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 Zolgensma. 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

Long-term safety of onasemnogene abeparvovec therapy is added as missing information for Itvisma

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 8-7 Clinical trial data of Hepatotoxicity for Zolgensma

Preferred term	Therapeutic i.v. dose (N=97) n (%)
Alanine aminotransferase increased	18 (18.6)
Aspartate aminotransferase increase	22 (22.7)
Gamma-glutamyl transferase increased	5 (5.2)
Transaminases increased	5 (5.2)
Liver function test increased	1 (1.0)
Hypertransaminasaemia	8 (8.2)
Hepatic steatosis	1 (1.0)

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

Table 8-8 Clinical trial data of Hepatotoxicity in Itvisma

Preferred term	Therapeutic IT dose, N=127, n (%)
Alanine aminotransferase increased	1 (0.8)
Aspartate aminotransferase increase	3 (2.4)

Hepatic enzyme increased	4 (3.1)
Hepatic function abnormal	2 (1.6)
Hepatitis	2 (1.6)
Hypertransaminasaemia	1 (0.8)

Data cut-off date: 27-May-2025
Source: [OAV101B SCS Appendix 1-Table 2-3.2.1]
MedDRA version 28.0

Table 8-9 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	**Zolgensma and Itvisma:** **Clinical trials**: Transaminase elevations have been observed without association with clinical signs or symptoms. **Zolgensma:** **Early access programs and post-marketing reports**: Adverse events of transaminase elevations are commonly reported following Zolgensma administration. In the post-marketing setting, several cases of ALF have been reported, some of which had fatal outcomes.
Characterization of the risk	**Zolgensma:** 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 symptoms. The incidence of hepatic adverse events in clinical trials as of 12-Nov-2020 is summarized in Table 8-7. 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 Zolgensma dosing. **Itvisma:** The incidence of hepatic adverse events in clinical trials as of 27-May-2025 is summarized in Table 8-8. No case of isolated liver failure was reported in clinical trials. In the 52-week pooled analysis, most of the patients experienced mild (Grade 1) and transient transaminase elevations which occurred approximately between weeks 6 and 12. No clinically meaningful changes in alkaline phosphatase, or bilirubin were seen through the end of Period 1 in either treatment arm [OAV101B SCS-Section 3.2.4.1].
Risk factors and risk groups	Patients with impaired liver function. Data from a small study with Zolgensma 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).

Hepatotoxicity	Details
	This is not expected with Itvisma as it will be administered as one-time intrathecal injection at a dose of 1.2 x 10^{14} vg irrespective of patients' age and weight.
Preventability	In order to mitigate potential for hepatotoxicity, patients should have liver function tests (such as ALT, AST, total bilirubin, albumin, prothrombin time [international normalized ratio; PT(INR)] and partial thromboplastin time [PTT]) conducted at baseline, and ALT, AST, total bilirubin should be monitored at regular intervals for at least 3 months following onasemnogene abeparvovec administration (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, PT(INR) and PTT). 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 administration. Pretreatment with oral prednisolone should be given 24 hours prior to administration 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.
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 because symptomatic hepatotoxicity is a rare occurrence.

8.3.1.2 Important identified risk: Transient thrombocytopenia

Table 8-10 Clinical trial data of Transient thrombocytopenia in Zolgensma

SMQ Preferred Term	Therapeutic IV dose (N=97) n (%)
Platelet count decreased	2 (2.1)
Thrombocytopenia	4 (4.1)

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

Table 8-11 Clinical trial data of Transient thrombocytopenia in Itvisma

Preferred Term	N=127
Thrombocytopenia	2 (1.6)
Platelet count decreased	1 (0.8)

Data cut-off date: 27-May-2025
Source: [OAV101B SCS Appendix 1-Table 2-3.2.1]
MedDRA version 28.0

Table 8-12 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	**Zolgensma:** **Clinical trials**: Transient thrombocytopenia was observed in Zolgensma clinical studies. In most cases, the lowest platelet value occurred the first week following Zolgensma infusion. **Early access programs and post-marketing reports**: Adverse events of thrombocytopenia or decreased platelet counts are commonly reported after Zolgensma administration. These events are generally not clinically significant. Post-marketing cases with platelet counts < 50 × 10^9/L and <25 × 10^9/L have been reported to occur within three weeks following Zolgensma administration. **Itvisma:** For the 52-week pooled analysis the earliest time point post baseline is Week 4 due to difference in the visit schedules in Studies B12301, B12302 and CL-102. Analyses of the individual studies show a small, transient decrease in platelet count within the first week post Itvisma dosing, with mean values returning to baseline thereafter in Study B12301 [OAV101B SCS-Section 3.1.3.2].
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

Transient thrombocytopenia	Details
	trials are summarized in Table 8-10 (Zolgensma) and in Table 8-11 (Itvisma).
Risk factors and risk groups	Data from a small study with Zolgensma, 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). This is not expected in Itvisma as it will be administered as one-time intrathecal injection at a dose of 1.2 x 10^{14} vg irrespective of patients age and weight.
Preventability	**Zolgensma:** Platelet counts should be obtained before Zolgensma 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. **Itvisma:** Platelet counts should be obtained before Itvisma injection and should be monitored on a regular basis afterwards, at least weekly for the first month and as clinically indicated 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 occurrence as a symptomatic condition.

8.3.1.3 Important identified risk: Thrombotic microangiopathy

Table 8-13 Important identified risk: Thrombotic microangiopathy

Thrombotic microangiopathy	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Zolgensma**: Cases of TMA were reported in 39 patients cumulatively up to 23-May-2024. Of these, in 18 patients, diagnosis of TMA was supported by available clinical details. All 18 confirmed TMA cases were reported within 1-2 weeks post Zolgensma 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

Thrombotic microangiopathy	Details
	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 diacylglycerol 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 Zolgensma and TMA is plausible. **Itvisma:** There were no cases of thrombotic microangiopathy reported to date in patients with Itvisma.
Characterization of the risk	**Zolgensma:** Of the 39 cases, TMA was well documented in 18 cases. All 18 well documented TMA cases were reported within 1-2 Weeks post Zolgensma intravenous infusion. In 18 patients, diagnosis of TMA was supported by available clinical details. Clinical characteristics for all cases remain similar. The majority of the patients were female. Concurrent infections were demonstrated in half of the patients. Recovery from TMA was reported in majority of cases. In some cases, laboratory test results normalized or progressively improved (i.e. platelet count, renal function tests, and hemoglobin values). CTCAE Grade 4 decrease in platelet counts was reported in majority of cases. Fatal outcome was reported for one patient in the subsequent clinical course consistent with septic shock, two weeks after TMA had clinically resolved following intensive care and hemofiltration. Invasive interventions (plasmapheresis, dialysis, hemofiltration or/and transfusions) were performed in half of the cases. **Itvisma:** There were no cases of thrombotic microangiopathy reported to date in patients with Itvisma. The benefit of Itvisma 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.

Thrombotic microangiopathy	Details
Risk factors and risk groups	Infections and recent vaccinations
Preventability	Prompt attention to signs and symptoms of TMA is advised, as TMA is a life-threatening condition which can result in fatal outcomes. Thrombocytopenia is a key feature of TMA, therefore platelet counts should be closely monitored within the first three to four weeks following administration 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 (applicable for Zolgensma only)

Table 8-14 Important potential risk: Cardiac adverse events (applicable for Zolgensma only)

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	Cardiac troponin-I was considered as a marker of potential cardiac toxicity and was measured in CL-101. It was not initially measured in CL-302, CL-306, or CL-304; however, protocol amendments were made to include measurement of cardiac troponin-I. Cardiac troponin-I was not collected in Study CL-303. In studies CL-101, CL-302, CL-303, CL-304, and CL-306, at least 1 cardiac troponin value was obtained from 22 patients and baseline values were obtained from 11 patients. However, cardiac troponin-I was not collected in all patients; some patients had cardiac troponin-I and/or -T performed at local laboratories as it was permitted as per protocol. Therefore, the data represented from these studies was a mixture of high-sensitive and normal

Cardiac adverse events	Details
	cardiac troponin values. Cardiac troponin-I was considered to be elevated when >0.05 ng/mL; it was not possible to calculate percentage change from baseline due to multiple missing values. From this limited data, it was observed that elevated cardiac troponin was reported in some patients at baseline; in other patients, increases were reported after treatment with Zolgensma. All but one elevation normalized by the Month 2 visit and the maximum value observed was 0.200 ng/mL. There were no remarkable findings on these studies related to CKMB or ECG in these studies. In the 5 years since the initial approval of Zolgensma, troponin-I monitoring has been indicated at baseline prior to infusion, weekly for the first month, then biweekly for months 2 and 3 after infusion. Troponin-I elevations have been detailed in previous versions of the PSUR, but no clinical symptoms related to these elevations have been reported. After Zolgensma dosing, some patients developed isolated elevations in troponin without associated signs/symptoms; the reported cardiac AEs in patients were considered of secondary etiology (e.g. respiratory dysfunction or sepsis leading to cardiac events).
Risk factors and risk groups	Underlying cardiac abnormalities
Preventability	Troponin I should be obtained before Zolgensma infusion and monitored as clinically indicated. 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 Zolgensma 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 (applicable for Zolgensma only)

Table 8-15 Important potential risk: Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required (applicable for Zolgensma only)

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 anti-AAV9 titres > 1:50 have not been studied in onasemnogene abeparvovec clinical studies. After administration of Zolgensma, increases in anti-AAV9 titres were observed. This is considered an expected response, and there were no apparent

Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required	Details
	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. All patients treated in clinical trials had anti-AAV9 titres ≤ 1:50 prior to administration of Zolgensma. 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 Zolgensma.
Preventability	Patients should be tested for the presence of anti-AAV9 antibodies prior to infusion with Zolgensma.
Impact on the benefit-risk balance of the product	Unknown.
Public health impact	Minimal due to the rarity of the condition

8.3.1.6 Important potential risk: Dorsal root ganglia toxicity/peripheral sensory neuropathy

Table 8-16 Important potential risk: Dorsal root ganglia toxicity/peripheral sensory neuropathy

Dorsal root ganglia toxicity/peripheral sensory neuropathy	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Zolgensma:** **Clinical**: No adverse events suggestive of ganglionopathy were observed in patients treated with Zolgensma 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/peripheral sensory neuropathy. 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, IT and IV 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

Dorsal root ganglia toxicity/peripheral sensory neuropathy	Details
	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 was 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. **Itvisma:** In the 52-week pooled analysis, signs and symptoms that may be suggestive of DRG toxicity AESI were reported in 4 patients. Two of these patients were in Study B12301 Itvisma arm, who experienced peripheral sensory neuropathies. The other two patients received Itvisma in Study B12302. The first case was paraesthesia in feet reported in a [redacted] within 28 days post dose and was considered as study treatment related, mild, resolved without any treatment, and was not a SAE. The second case was sensory disturbance on bilateral forearms, neck, and scalp reported in a [redacted] within 38 days post dose, lasting 2 days and was considered as not related to study treatment, mild, resolved without any treatment, and was not a SAE [OAV101B SCS-Section 2.7.5]. In the long-term safety analysis, no AESI of signs and symptoms that may be suggestive of DRG toxicity were reported [OAV101B SCS-Section 2.7.5]. No biopsy was performed in these patients to assess whether microscopic changes consistent with DRG toxicity were present. Based on currently available data, it is not possible to determine whether these symptoms were the result of a sensory neuropathy, or of a sensory neuronopathy / ganglionopathy. Complete neurological evaluation and other testing and/or symptom management should be considered based on the patient's clinical presentation.
Characterization of the risk	Unknown
Risk factors and risk groups	Unknown
Preventability	Unknown
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 8-17 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 potential integration of the AAV vector DNA of onasemnogene abeparvovec into the host 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	**Zolgensma and Itvisma:** 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 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

Risk of tumorigenicity due to chromosomal integration	Details
	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-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. **Study AVXS-101-LT-001 (Zolgensma study)** 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. **Itvisma**: In the 52-week pooled analysis, there were no relevant reports of malignancies [OAV101B SCS-Section 2.7.6]. **Study COAV101A12308 (Itvisma study)** In Study A12308, 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 8-18 Missing information: Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only)

Long-term efficacy of onasemnogene abeparvovec therapy	Details
Evidence source	Long-term follow-up data in SMA patients treated with Zolgensma are available from 2 long-term follow-up studies LT-001 and LT-002. Both studies consist of a 5-year follow-up phase, followed by an observational phase, and the total duration of each study is 15 years after dosing in the parent study.
Population in need of further characterization	In Study LT-001, all participants had completed the first 5 years of follow-up at the time of the cut-off date (01-Jul-2024); the observational phase of this study is ongoing. For Study LT-002, the 5-year follow-up phase is ongoing, and data up to the cut-off date of 24-Jun-2024 have been analyzed. Study LT-001 enrolled 13 participants from study AVXS-101-CL-101, the first-in-human study of Zolgensma administered intravenously: 3 from the low-dose cohort (Zolgensma dose of 6.7×10^{13} vg/kg), and 10 from the proposed therapeutic dose cohort (Zolgensma dose of 1.1×10^{14} vg/kg). Eight of the 13 participants were ongoing, and 5 had discontinued at the time of data cut-off. The median follow-up time since dosing in the parent study CL 101 was 9.85 years (min-max: 9.8-10.1 years) in the low dose cohort, and 8.63 years (min-max: 6.8-9.6 years) in the therapeutic dose cohort. Study LT-002 enrolled 68 participants who received the Zolgensma dose of 6.7×10^{13} vg/kg in a parent clinical study. Of the 68 Zolgensma-treated participants, 58 participants (85.3%) were ongoing at the time of data cut-off and the remainder had discontinued. The median follow-up time since dosing with Zolgensma in the parent studies was 5.53 years (min-max: 2.8-6.6 years). In both studies LT-001 and LT-002, the type of SAEs reported were generally typical of those seen in children with SMA. The most frequently reported events were in the SOC Infections and infestations, followed by respiratory, thoracic and mediastinal disorders. No deaths and no SAEs related to study treatment were reported in LT-001. In LT-002 one death, not considered related to study treatment, was reported. The majority of SAEs reported in LT-002 were not related to study treatment; events considered related to study treatment by the investigator were reported in 2 participants. No late-onset events emerged in either of these long-term follow-up studies (Study LT-001 and Study LT-002).

Table 8-19 Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)

Long term safety of onasemnogene abeparvovec therapy	Details
Evidence source	Long-term follow-up data in SMA patients treated with Itvisma are available from 2 long-term follow-up studies LT-002 and COAV101A12308. LT-002 consists of a 5-year follow-up phase, followed by an observational phase with a total duration of 15 years after dosing in the parent study. COAV101A12308 is a long-term follow-up study with a duration of 5 years following enrolment in the long-term study.
Population in need of further characterization	As of 24-Jun-2024, study LT-002 enrolled 18 participants who received Itvisma at a dose of 1.2×10^{14} vg in Study CL-102. The median follow-up time since dosing in study CL-102 was 5.32 years (min-max: 2.9-6.4 years) (Study LT-002). As of 05-Nov-2024, study COAV101A12308 enrolled 59 participants treated with Itvisma in Phase 3 studies COAV101B12301 or COAV101B12302 (OAV101B SCS). No late-onset events emerged in either of these long-term follow-up studies (Study LT-002 and OAV101B SCS).

Table 8-20 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 (applicable for Zolgensma only)

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 Zolgensma in patients with SMA types 2 and 3.

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

Table 9-1 Part II SVIII.1: Summary of safety concerns (applicable for Zolgensma and Itvisma)

Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events (applicable for Zolgensma only) • Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required (applicable for Zolgensma only) • Dorsal root ganglia toxicity/peripheral sensory neuropathy • Tumorigenicity due to chromosomal integration
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only) • Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only) • 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 (applicable for Zolgensma only)

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) – each checklist is applicable for Zolgensma or Itvisma) will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- **Hepatotoxicity**
  Onasemnogene abeparvovec elevated liver enzymes checklist
- **Transient thrombocytopenia**
  Onasemnogene abeparvovec decreased platelet count checklist
- **Thrombotic microangiopathy**
  Onasemnogene abeparvovec thrombotic microangiopathy (TMA) checklist
- **Cardiac adverse events (applicable for Zolgensma only)**
  Onasemnogene abeparvovec cardiac adverse events checklist
- **Dorsal root ganglia toxicity/peripheral sensory neuropathy**
  Onasemnogene abeparvovec sensory neuropathies checklist

Other forms of routine pharmacovigilance activities for risks

None.

10.2 Part III.2. Additional pharmacovigilance activities

AVXS-101-LT-001 (applicable for Zolgensma only):

A LTFU 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 LTFU 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 LTFU study of patients in the clinical trials for receiving onasemnogene abeparvovec

Rationale and study objectives:

To collect LTFU 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

COAV101A12308 (applicable for Itvisma only): A LTFU study of patients with SMA who were treated with OAV101 IT or OAV101 IV in clinical trials.

Rationale and study objectives:

To collect LTFU safety and monitoring of efficacy in patients with SMA who were treated with onasemnogene abeparvovec in clinical trials.

Study design:

Interventional

Study population:

Patients diagnosed with SMA who participated in OAV101 clinical trials

Milestones:

- Study Report: Q3 2031

SMA Registries Feasibility Assessment (applicable for Itvisma only):

The overall objective of this feasibility assessment is to evaluate, in a structured manner, whether data from existing SMA registries are fit for purpose to evaluate the following in patients administered Itvisma:

- The incidence, risk factors, clinical course, and outcome of peripheral sensory neuropathy.
- Long-term patient follow-up (up to 15 years) with focus on the risk of tumorigenicity due to chromosomal integration.

- If effectiveness measures are routinely collected and available in the population not studied in the clinical studies. Of note, among patients with SMA Type 3 or 4, the maximum motor function is typically walking independently; thus, the effectiveness of treatment would be stabilization of maintenance of walking.

Milestones:

- Submission of a feasibility outcome report: within 3 months following the marketing authorization approval.
- Submission of a registry-based study protocol or alternative proposal as post-authorization measure: To be confirmed following consultation with EMA.

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 (applicable for Zolgensma only) Ongoing	To collect LTFU 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/peripheral sensory neuropathy • Tumorigenicity due to chromosomal integration • Long-term efficacy of onasemnogene abeparvovec therapy	Final study report	Q4 2033

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study AVXS-101-LT-002 Ongoing	To collect LTFU 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 (applicable for Zolgensma only) • Dorsal root ganglia toxicity/peripheral sensory neuropathy • Tumorigenicity due to chromosomal integration • Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only) • Long-term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)	Final study report	Q3 2036
COAV101A12308 (applicable for Itvisma only) Ongoing	To collect LTFU safety and monitoring of efficacy in patients with SMA who were treated with OAV101 in clinical trials.	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy • Dorsal root ganglia toxicity/peripheral sensory neuropathy • Tumorigenicity due to chromosomal integration • Long-term safety of onasemnogene abeparvovec therapy	Final study report	Q3 2031
SMA Registries Feasibility Assessment	To evaluate, in a structured manner, whether data from existing SMA registries is fit for	• Dorsal root ganglia toxicity/Peripheral sensory neuropathy	Submission of a feasibility outcome report	Within 3 months following the marketing

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(applicable for Itvisma only) Planned	purpose, to evaluate: the incidence, risk factors, clinical course, and outcome of peripheral sensory neuropathy, long-term patient follow-up (up to 15 years) with focus on the risk of tumorigenicity due to chromosomal integration and if effectiveness measures are routinely collected and available in the population not included in the clinical studies (SMA Type 3 or 4).	• Tumorigenicity due to chromosomal integration		authorisation approval
			Submission of a registry-based study protocol or alternative proposal as post-authorization measure	To be confirmed following consultation with EMA

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 (applicable for Zolgensma only) 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 (applicable for Zolgensma and Itvisma)

Safety concern	Routine risk minimization activities
Hepatotoxicity (applicable for Zolgensma and Itvisma)	**Routine risk communication:** **Zolgensma** SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3 **Zolgensma** PL Sections 2, 3, 4 **Itvisma** SmPC Sections 4.2, 4.4, 4.8, 5.3 **Itvisma** 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 Sections 2, 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 (applicable for Zolgensma and Itvisma)	**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 (applicable for Zolgensma and Itvisma)	**Routine risk communication:** **Zolgensma** SmPC Sections 4.2, 4.4, 4.8 **Zolgensma** PL Sections 2, 4 **Itvisma** SmPC Sections 4.2, 4.4 **Itvisma** PL Sections 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	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 :** None
Cardiac adverse events (applicable for Zolgensma only)	**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 (applicable for Zolgensma only)	**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 Zolgensma (SmPC Section 4.4) **Other routine risk minimization measures beyond the Product Information:** None
Dorsal root ganglia toxicity/peripheral sensory neuropathy (applicable for Zolgensma and Itvisma)	**Routine risk communication:** **Zolgensma** SmPC Section 5.3 **Zolgensma** PL: None **Itvisma** SmPC Sections 4.4, 4.8, 5.3 **Itvisma** PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** **Zolgensma**: None **Itvisma:** Section 4.4 of the SmPC provides recommendation on neurological evaluation and other testing and/or symptom management. It also recommends the need for patients and caregivers to be informed about the signs and symptoms of peripheral sensory neuropathy and be advised to notify their physician promptly if such symptoms occur. PL Section 2 provides information about the signs of peripheral sensory neuropathy and advises to notify their physician promptly if such signs occur.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: None
Tumorigenicity due to chromosomal integration (applicable for Zolgensma and Itvisma)	**Routine risk communication:** SmPC Section 4.4 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 abeparvovec therapy (applicable for Zolgensma only)	**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
Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)	**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
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 (applicable for Zolgensma only)	**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

The following educational materials are applicable and will be made available separately for Zolgensma and Itvisma:

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
- Transient thrombocytopenia
- Thrombotic microangiopathy
- Dorsal root ganglia toxicity/peripheral sensory neuropathy (applicable for Itvisma only)

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/Itvisma.

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

The effectiveness of risk mitigation of hepatotoxicity, transient thrombocytopenia, thrombotic microangiopathy and dorsal root ganglia toxicity/peripheral sensory neuropathy (applicable for Itvisma only) will be assessed in the context of risk evaluation in the PSUR.

Educational material

Caregiver information guide (applicable for Zolgensma)

Patient/patient’s caregiver information guide (applicable for Itvisma)

Objectives:

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

- Hepatotoxicity
- Transient thrombocytopenia (low platelet count)
- Thrombotic microangiopathy
- Dorsal root ganglia toxicity/peripheral sensory neuropathy (applicable for Itvisma only)

- 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 minimization measures and criteria for success.

The effectiveness of risk mitigation of hepatotoxicity, transient thrombocytopenia (low platelet count), thrombotic microangiopathy and dorsal root ganglia toxicity/peripheral sensory neuropathy (applicable for Itvisma only) 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 (applicable for Zolgensma and Itvisma)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimization measures**: **Zolgensma** SmPC Sections 4.2, 4.4, 4.8. 5.2, 5.3 **Zolgensma** PL Sections 2, 3, 4 **Itvisma** SmPC Sections 4.2, 4.4, 4.8, 5.3 **Itvisma** PL Sections 2, 3, 4 **Additional risk minimization measures**: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (applicable for Zolgensma and Itvisma)**: Targeted follow up questionnaire **Additional pharmacovigilance activities**: **Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308
Transient thrombocytopenia	**Routine risk minimization measures (applicable for Zolgensma and Itvisma)**: SmPC Sections 4.2, 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (applicable for Zolgensma and Itvisma)**:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL Sections 2, 4	Targeted follow up questionnaire
	Additional risk minimization measures: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)	**Additional pharmacovigilance activities**: **Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308
Thrombotic microangiopathy	**Routine risk minimization measures**: **Zolgensma** SmPC Sections 4.2, 4.4, 4.8 **Zolgensma** PL Sections 2, 4 **Itvisma** SmPC Sections 4.2, 4.4 **Itvisma** PL Sections 2, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (applicable for Zolgensma and Itvisma)**: Targeted follow up questionnaire **Additional pharmacovigilance activities**: **Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308
	Additional risk minimization measures: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)	
Cardiac adverse events (applicable for Zolgensma only)	**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 pharmacovigilance activities**: AVXS-101-LT-001 and AVXS-101-LT-002
	Additional risk minimization measures: None	
Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required (applicable for Zolgensma only)	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8 **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Dorsal root ganglia toxicity/peripheral	**Routine risk minimization measures**: **Zolgensma** SmPC Section 5.3 **Zolgensma** PL: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (applicable for Zolgensma and Itvisma)**:

Safety concern	Risk minimization measures	Pharmacovigilance activities
sensory neuropathy	**Itvisma** SmPC Sections 4.4, 4.8, 5.3 **Itvisma** PL Section 2 **Additional risk minimization measures**: Healthcare professional guide (applicable for Itvisma only) Patient/patient's caregiver information guide (applicable for Itvisma only)	Targeted follow up questionnaire **Additional pharmacovigilance activities**: **Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002, COAV101A12308 and SMA registries feasibility assessment
Tumorigenicity due to chromosomal integration	**Routine risk minimization measures (applicable for Zolgensma and Itvisma)**: SmPC Section 4.4 PL Section 2 **Additional risk minimization measures (applicable for Zolgensma and Itvisma):** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (applicable for Zolgensma and Itvisma)**: None **Additional pharmacovigilance activities**: **Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma***:* AVXS-101-LT-002, COAV101A12308 and SMA registries feasibility assessment
Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only)	**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
Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)	**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-002 and COAV101A12308
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 (applicable for Zolgensma only)	**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

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

Zolgensma and Itvisma's respective summary of product characteristics (SmPC) and the corresponding package leaflets give essential information to healthcare professionals and patients on how Zolgensma and Itvisma should be used.

This summary of the integrated RMP for Zolgensma and Itvisma 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 the integrated Zolgensma and Itvisma'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.

Itvisma is indicated for the treatment of 5q SMA with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older.

Itvisma is administered as a single dose of 1.2×10^{14} vg. For intrathecal injection.

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.

Further information about the evaluation of Itvisma's benefits can be found in Itvisma'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/itvisma.

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

Important risks of Zolgensma and Itvisma, together with measures to minimize such risks and the proposed studies for learning more about Zolgensma's and Itvisma'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 or Itvisma 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 and Itvisma 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 and Itvisma. 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 (for Zolgensma and Itvisma)	
Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events (applicable for Zolgensma only) • Use in patients with anti-AAV9 antibody titers > 1:50 and higher vector loads required (applicable for Zolgensma only) • Dorsal root ganglia toxicity/peripheral sensory neuropathy • Tumorigenicity due to chromosomal integration
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy (applicable for Zolgensma only) • Long term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only) • 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 (applicable for Zolgensma only)

13.2.2 Part VI: II B: Summary of important risks

Table 13-2 Important identified risk: Hepatotoxicity (applicable for Zolgensma and Itvisma)

Evidence for linking the risk to the medicine	**Zolgensma and Itvisma:** **Clinical trials**: Transaminase elevations have been observed without association with clinical signs or symptoms. **Zolgensma:** **Early access programs and post-marketing reports**: Adverse events of transaminase elevations are commonly reported following Zolgensma administration. In the post-marketing setting, cases of ALF have been reported, some of which had fatal outcomes.
Risk factors and risk groups	**Zolgensma:** 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). **Itvisma:** Not expected as it will be administered as one-time intrathecal injection at a dose of 1.2×10^{14} vg irrespective of patients age and weight.
Risk minimization measures	**Routine risk minimization measures**: **Zolgensma** SmPC Sections 4.2, 4.4, 4.8. 5.2, and 5.3 **Zolgensma** Package leaflet (PL) Sections 2, 3, 4 **Itvisma** SmPC Sections 4.2, 4.4, 4.8, 5.3 **Itvisma** PL Sections 2, 3, 4 **Additional risk minimization measures**: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)
Additional pharmacovigilance activities	**Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: Transient thrombocytopenia (applicable for Zolgensma and Itvisma)

Evidence for linking the risk to the medicine	**Zolgensma:** **Clinical trials**: Transient thrombocytopenia was observed in Zolgensma clinical studies. In most cases, the lowest platelet value occurred the first week following Zolgensma infusion. **Early access programs and post-marketing reports**: Adverse events of thrombocytopenia or decreased platelet counts are

	commonly reported after Zolgensma 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 Zolgensma administration. **Itvisma:** **Clinical trials:** The incidence of transient thrombocytopenia events. Analyses of the studies show a small transient decrease in platelet count within the first week post Itvisma dosing, with mean values returning to baseline thereafter in Study B12301.
Risk factors and risk groups	**Zolgensma:** 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. **Itvisma:** Not expected as it will be administered as one-time intrathecal injection at a dose of 1.2 x 10^{14} vg irrespective of patients age and weight.
Risk minimization measures	**Routine risk minimization measures (applicable for Zolgensma and Itvisma)**: SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 4 **Additional risk minimization measures**: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)
Additional pharmacovigilance activities	**Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-4 Important identified risk: Thrombotic microangiopathy (applicable for Zolgensma and Itvisma)

Evidence for linking the risk to the medicine	**Zolgensma:** Cases of TMA were reported in 39 patients in the post-marketing setting, early access programs, and the registry, cumulatively up to DLP 23-May-2024. Of these, in 18 patients, diagnosis of TMA was supported by available clinical details. All 18 confirmed TMA cases were reported within 1-2 weeks post Zolgensma 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 diacylglycerol kinase and/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 Zolgensma and TMA is plausible. **Itvisma:** There were no cases of thrombotic microangiopathy reported in patients treated with Itvisma.
Risk factors and risk groups	**Zolgensma and Itvisma*:*** Infections and recent vaccinations
Risk minimization measures	**Routine risk minimization measures**: **Zolgensma** SmPC Sections 4.2, 4.4, 4.8 **Zolgensma** PL Sections 2, 4 **Itvisma** SmPC Sections 4.2, 4.4 **Itvisma** PL Sections 2, 4 **Additional risk minimization measures**: Healthcare professional guide (applicable for Zolgensma and Itvisma) Caregiver information guide (applicable for Zolgensma) Patient/patient's caregiver information guide (applicable for Itvisma)
Additional pharmacovigilance activities	**Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002 and COAV101A12308 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 (applicable for Zolgensma only)

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 (applicable for Zolgensma only)

Evidence for linking the risk to the medicine	**Clinical**: Patients with anti-AAV9 titres > 1:50 have not been studied in Zolgensma clinical studies. After administration of Zolgensma, 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 Zolgensma.
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/peripheral sensory neuropathy (applicable for Zolgensma and Itvisma)

Evidence for linking the risk to the medicine	**Zolgensma:** **Clinical**: No adverse events suggestive of ganglionopathy were observed in patients treated with Zolgensma 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, IT and IV 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. **Itvisma:** Signs and symptoms that may be suggestive of DRG toxicity AESI were reported in 4 patients. In the long-term safety analysis, no AESI of signs and symptoms that may be suggestive of DRG toxicity were reported.
Risk factors and risk groups	**Zolgensma and Itvisma:** Unknown
Risk minimization measures	**Routine risk minimization measures**: **Zolgensma** SmPC Section 5.3 **Zolgensma** PL: None **Itvisma** SmPC Sections 4.4, 4.8, 5.3 **Itvisma** PL Section 2 **Additional risk minimization measures**: Healthcare professional guide (applicable for Itvisma only) Patient/patient's caregiver information guide (applicable for Itvisma only)
Additional pharmacovigilance activities	**Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002, COAV101A12308 and SMA registries feasibility assessment 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 (applicable for Zolgensma and Itvisma)

Evidence for linking the risk to the medicine	**Zolgensma and Itvisma:** There is a theoretical risk of tumorigenicity due to potential integration of the AAV vector DNA of onasemnogene abeparvovec into the host 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	**Zolgensma and Itvisma:** Unknown

Risk minimization measures	**Routine risk minimization measures (applicable for Zolgensma and Itvisma):** SmPC Section 4.4 PL Section 2 **Additional risk minimization measures (applicable for Zolgensma and Itvisma):** None
Additional pharmacovigilance activities	**Zolgensma**: AVXS-101-LT-001 and AVXS-101-LT-002 **Itvisma**: AVXS-101-LT-002, COAV101A12308 and SMA registries feasibility assessment. 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 (applicable for Zolgensma only)

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: Long-term safety of onasemnogene abeparvovec therapy (applicable for Itvisma only)

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None
Additional pharmacovigilance activities	AVXS-101-LT-002 and COAV101A12308

Table 13-11 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 (applicable for Zolgensma only)

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 13-12 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) (applicable for Zolgensma only)	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 13-13 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
AVXS-101-LT-001: LTFU study for patients from AVXS-101-CL-101 (START) (applicable for Zolgensma only).	To collect LTFU 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 LTFU 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.
COAV101A12308: A LTFU study of patients with SMA who were treated with OAV101 IT or OAV101 IV in clinical trials (applicable for Itvisma only).	To collect LTFU safety and monitoring of safety and efficacy in patients with SMA who were treated with onasemnogene abeparvovec in clinical trials.
SMA Registries Feasibility Assessment (applicable for Itvisma only).	To evaluate, in a structured manner, whether data from existing SMA registries is fit for purpose, to evaluate: the incidence, risk factors, clinical course, and outcome of peripheral sensory neuropathy, long-term patient follow-up (up to 15 years) with focus on the risk of tumorigenicity due to chromosomal integration and if effectiveness measures are routinely collected and available in the population not included in the clinical studies (SMA Type 3 or 4).

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Hepatotoxicity

Onasemnogene abeparvovec elevated liver enzymes checklist (v5.0/Apr2025)

NOVARTIS

Argus ID # _____

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

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. Please provide as much detail as possible.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of administration	Route	SMA type/ SMA status
						☐ Intrathecal ☐ Intravenous Dose:	

1. **Please provide up to the last two liver test results *PRIOR* to administration of Onasemnogene abeparvovec. 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 Onasemnogene abeparvovec.**

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

NOVARTIS

Argus ID # _____

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

	Test	Date	Value	Expected Normal range	Not performed
after administration of Onasemnogene abeparvovec	ALT				☐
	Bilirubin total				☐
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
☐ Dark urine
☐ Pale stool
☐ Pruritus
☐ Nausea or vomiting
☐ Hepatosplenomegaly
☐ Ascites
☐ Fever
☐ Fatigue
☐ Bleeding (specify location)
☐ Other (specify)
☐ Asterixis (flapping tremor)
☐ Altered mental status
☐ Abdominal pain (incl. location)
☐ Anorexia or loss of appetite
☐ None

Please provide further details below: _____

4. Were any of the following diagnostic tests performed?

Tests	Before administration of Onasemnogene abeparvovec		After administration of Onasemnogene abeparvovec		Normal range (if applicable)
	Date	Results	Date	Results	
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

NOVARTIS

Argus ID # _____

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

Test	Date	Result	Not available
Anti-AAV9 antibody			☐

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 Onasemnogene abeparvovec 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

13. Could you please confirm the final diagnosis?

NOVARTIS

Argus ID # _____

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

____

Transient thrombocytopenia

Onasemnogene abeparvovec decreased platelet count checklist (v4.0/Apr2025)

NOVARTIS

Argus ID # _____

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

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. Please provide as much detail as possible.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of administration	Route	SMA type/ SMA status
						☐ Intrathecal ☐ Intravenous Dose:	

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 Onasemnogene abeparvovec				☐
First platelet count below normal range after administration of Onasemnogene abeparvovec				☐
Lowest platelet count after administration of Onasemnogene abeparvovec				☐
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 parameter** ☐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 Onasemnogene abeparvovec 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**

_____
_____
_____
_____
_____

11. **Could you please confirm the final diagnosis?**

_____

Thrombotic microangiopathy

Onasemnogene abeparvovec thrombotic microangiopathy (TMA) checklist (v4.0/Apr2025)

NOVARTIS

ARGUS ID #:_____

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

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. Please provide as much detail as possible.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of administration	Route	SMA type/ SMA status
						☐ Intrathecal ☐ Intravenous Dose:	

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 Onasemnogene abeparvovec (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 Onasemnogene abeparvovec			After administration of Onasemnogene abeparvovec		
		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		

NOVARTIS

ARGUS ID #:_____

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

Conditions/Events	2 months before administration of Onasemnogene abeparvovec			After administration of Onasemnogene abeparvovec		
		Date	Description		Date	Description
Any illnesses (define pathogen):	☐ Yes ☐ No			☐ Yes ☐ No		

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

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 Onasemnogene abeparvovec.

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				☐

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
CH50eq				☐
Alternative pathway functional assay				☐
Hemolytic assay				☐
FH autoantibody				☐
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 Onasemnogene abeparvovec 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*): ___/_____/_____

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

10. Please describe any other relevant information.

11. Could you please confirm the final diagnosis?

Cardiac adverse events (applicable for Zolgensma only)

Onasemnogene abeparvovec cardiac adverse events checklist (v4.0/Apr2025)

NOVARTIS

Argus ID #

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

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. Please provide as much detail as possible.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of administration	Route	SMA type/ SMA status
						☐ Intrathecal ☐ Intravenous Dose:	

1. **Cardiac Event Description:**

Diagnosis	Date of diagnosis	Contributing factors/ comorbidities	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 Onasemnogene abeparvovec		After administration of Onasemnogene abeparvovec		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 Onasemnogene abeparvovec		After administration of Onasemnogene abeparvovec		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. **Please list any medical history _ concomitant medical conditions below**

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		

NOVARTIS

Argus ID #

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

Dose	Amount administered	Date
7		

7. **Please provide the interval between last Nusinersen dose and Onasemnogene abeparvovec administration:**

_____

8. **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.**

_____

_____

_____

_____

10. **Could you please confirm the final diagnosis?**

_____

Dorsal root ganglia toxicity/peripheral sensory neuropathy

Onasemnogene abeparvovec sensory neuropathies checklist (v3.0/Apr2025)

NOVARTIS

ARGUS ID #:_____

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

Onasemnogene abeparvovec
Sensory Neuropathies 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. Please provide as much detail as possible.

Patient identifier	Date of birth	Age at the time of administration	Gender (M / F)	Weight at time of administration (kg)	Date of administration	Route	SMA type/ SMA status
						☐ Intrathecal ☐ Intravenous Dose:	

1. **Event Description:**

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

☐ Paresthesia, Dysesthesia ☐ Thermesthesia ☐ Loss of proprioception/vibratory sense
☐ Hyperesthesia ☐ Anesthesia ☐ Absent tendon reflex
☐ Hypoesthesia ☐ Pain ☐ Areflexia

☐ Distal sensory disorders
(please specify)

_____
_____

☐ Sensory ataxia with balance disorders
(please specify)

_____
_____

☐ Autonomic disorders *(please specify and describe below the following symptoms: orthostatic hypotension, constipation, diarrhea, bladder disturbances, abnormal sweating and/or and pupil abnormalities)*

_____
_____

☐ None of the above

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

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

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

☐ Electromyoneurography (EMNG) ☐ Autonomic testing ☐ CSF analysis
☐ Nerve conduction studies ☐ MRI of spinal cord ☐ Skin biopsy
☐ Neurological examination (sensory exam, motor exam, deep tendon reflexes) ☐ 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

NOVARTIS

ARGUS ID #:_____

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

Please provide any other signs or symptoms and/or any other tests:

_____

_____

_____

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

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 Onasemnogene abeparvovec administration:

_____

3. Could you please confirm the final diagnosis?

_____

Annex 6 - Details of proposed additional risk minimization activities

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 (NOTE: Tradename is updated for each product: Zolgensma or Itvisma):

- Before the start of treatment:
  - Evaluate the patient's vaccination schedule;
  - [For Zolgensma] 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; about the importance of corticosteroid medicine; practical advice concerning bodily waste disposal; [For Itvisma] Inform the caregiver(s) about the main risks with Itvisma and their signs and symptoms, including hepatotoxicity, thrombocytopenia, TMA and peripheral sensory neuropathy ; about the need for regular blood sampling; about the importance of corticosteroids;
  - Inform the caregiver(s) of the need for increased vigilance in the prevention, monitoring, and management of infection before and after Tradename administration;
  - Patients should be tested for the presence of AAV9 antibodies.
- At the time of treatment:
  - Check if the overall health status of the patient is suitable for administration of Tradename (e.g. resolution of infections) or if a postponement is warranted;
  - Check that corticosteroid treatment was started before the administration of Tradename;
- After treatment:
  - 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;
  - [For Zolgensma] If patients do not respond adequately to corticosteroids, or if liver injury is suspected, HCP should consult a paediatric gastroenterologist or hepatologist; [For Itvisma] If patients do not respond adequately to corticosteroids, or if liver injury is suspected, HCP should consult a gastroenterologist or hepatologist;
  - [For Zolgensma] If TMA is suspected, a specialist should be consulted. [For Itvisma] If TMA is suspected, a haematologist and/or nephrologist should be consulted.
  - [For Itvisma] Patients and caregivers should be informed about the signs and symptoms of peripheral sensory neuropathy and be advised to notify their physician promptly if such symptoms occur. If peripheral sensory neuropathy is suspected, complete

neurological evaluation and other testing and/or symptom management should be considered based on the patient's clinical presentation.

Patient Information Pack

Package Leaflet

Caregiver information guide (applicable for Zolgensma)

Patient/patient's caregiver information guide (applicable for Itvisma)

The patient/patient's caregiver information guide shall contain the following key messages (NOTE: Tradename is updated for each product: Zolgensma or Itvisma):

- What is SMA.
- What is Tradename and how it works.
- Understanding the risks of Tradename.
- Treatment with Tradename: important information before, on the day of treatment 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 Tradename treatment, otherwise treatment may need to be postponed.
- [For Zolgensma and Itvisma] Tradename may increase the risk of abnormal clotting of blood in small blood vessels (thrombotic microangiopathy). [For Zolgensma] Cases generally occurred within the first two weeks after onasemnogene abeparvovec infusion. [For Zolgensma and Itvisma] Thrombotic microangiopathy is serious and may lead to death. Tell your or your child's doctor immediately if you notice signs and symptoms such as bruising, seizures or decrease in urine output. [For Zolgensma] 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. [For Itvisma] You or your child will have a regular blood test to check any decrease of platelets, the cells responsible for clotting, at least weekly for the first month after treatment. [For Zolgensma and Itvisma] Depending on the values and other signs and symptoms, further evaluations may be required.
- [For Zolgensma and Itvisma] Tradename can lower blood-platelet counts (thrombocytopenia). [For Zolgensma] Cases generally occurred within the first three weeks after onasemnogene abeparvovec infusion. [For Itvisma] Cases generally occurred within the first week after the patient was given Itvisma. [For Zolgensma] 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. [For Itvisma] Possible signs of a low blood-platelet count you need to look out for after you or your child is given Itvisma include abnormal bruising or bleeding. Speak to your or your child's doctor if you see signs such as bruising or bleeding for longer than usual if you or your child has been hurt.
- [For Zolgensma and Itvisma] Tradename can lead to an increase in enzymes (proteins found within the body) produced by the liver. In some cases, Tradename can affect the function of the liver and lead to injury of the liver. [For Zolgensma] Injury to the liver can lead to serious outcomes, including liver failure and death. [For Zolgensma] 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. [For Itvisma] Possible signs you need to look out for after you or 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 or your child's doctor straight away if you notice any symptoms suggestive of injury to the liver. You or your child will have a blood test to check how well the liver is working before starting treatment with Itvisma. You or 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.

- [For Zolgensma] 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. [For Itvisma] You or your child will be given a corticosteroid medicine such as prednisolone before treatment with Itvisma, and for about 2 months or longer after Itvisma treatment. The corticosteroid medicine will help manage effects of Itvisma such as increase in liver enzymes that you or your child could develop after treatment with Itvisma.
- [For 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. [For Itvisma] Tell your or your child's doctor in the event of vomiting before or after treatment with Itvisma, to make sure that you or your child does not miss corticosteroid dosing
- Before and after treatment with Tradename it is important to prevent infections by avoiding situations that may increase the risk of the patient 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 straight away in case of signs and symptoms suggestive of infection, such as respiratory infection (coughing, wheezing, sneezing, runny nose, sore throat or fever) prior to administration as the administration may need to be delayed until the infection is resolved, or after treatment with Tradename as it may lead to medical complications that may require urgent medical attention.
- [For Itvisma] Tell your or your child's doctor immediately if you or your child experience numbness, tingling, prickling or pain in the arms, hands, legs and/or feet after being given Itvisma. These may be signs of peripheral sensory neuropathy.
- Useful further information (supportive care, local associations).
- Contacts of the physician/prescriber.