ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Itvisma 1.2×10^{14} vector genomes solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter.

Onasemnogene abeparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each single-dose vial contains 1.2×10^{14} vector genomes (vg) of onasemnogene abeparvovec in 3 mL of solution. Onasemnogene abeparvovec intrathecal injection has a nominal concentration of 4×10^{13} vg/mL, and each vial contains an extractable volume of not less than 3 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
A clear to slightly opaque, colourless to faint white solution with a pH of 7.7 to 8.3 and osmolality of 390 to 430 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Before administration of Itvisma, baseline laboratory testing is required, including, but not limited to:
- AAV9 antibody testing using an appropriately validated assay (see section 4.4),
- liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (see section 4.4),
- creatinine, and
- complete blood count (including haemoglobin and platelet count) (see section 4.4).

It is recommended that patients are clinically stable in their overall health status prior to injection (see section 4.4). The benefit-risk profile of Itvisma in patients with respiratory failure, on permanent ventilation, and/or unable to swallow is not established.

Because the treatment persists in non-dividing cells, patients previously treated with onasemnogene abeparvovec (any route of administration) should not be treated with Itvisma (see section 5.1).

Posology

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

Immunomodulatory regimen
To dampen an immune response, immunomodulation with corticosteroids is recommended. Elevations in liver aminotransferases or decreased platelet counts may occur following treatment (see sections 4.4 and 4.8). Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Itvisma injection (see section 4.5).

Table 1 shows the recommended immunomodulatory regimen prior to and following injection.

Table 1 Recommended immunomodulatory regimen pre- and post-injection

Pre-injection	24 hours prior to Itvisma injection	Prednisolone orally 1 mg/kg/day (or equivalent)
Post-injection	30 days (including the day of Itvisma administration)	Prednisolone orally 1 mg/kg/day (or equivalent)
	Followed by 28 days: *For patients with unremarkable findings (normal clinical exam, total bilirubin, and whose ALT and AST values are both below 2 × upper limit of normal (ULN)) at the end of the 30 days period:* **or** *For patients with liver function abnormalities at the end of the 30 days period: continuing until the AST and ALT values are below 2 × ULN and all other assessments (e.g. total bilirubin) return to normal range, followed by tapering over 28 days or longer if needed.*	Systemic corticosteroids should be tapered gradually. Taper prednisolone (or equivalent if another corticosteroid is used), e.g. by decrements of 0.20 mg/kg/day per week over at least 4 weeks for oral prednisolone Systemic corticosteroids (equivalent to oral prednisolone 1 mg/kg/day) Systemic corticosteroids should be tapered gradually.

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 gastroenterologist or hepatologist and adjustment to the recommended immunomodulatory regimen, including increased dose, longer duration or prolongation of corticosteroid taper, may be considered (see section 4.4). If oral corticosteroid therapy is not tolerated or not effective, intravenous corticosteroids may be considered as clinically indicated.

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

Special populations
Renal impairment
The safety and efficacy of Itvisma have not been established in patients with renal impairment. A dose adjustment should not be considered.

Hepatic impairment
Itvisma therapy should be carefully considered in patients with hepatic impairment (see section 4.4). A dose adjustment should not be considered.

Paediatric population
The safety and efficacy of Itvisma in children aged under 2 years have not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made in children aged 6 months to < 2 years. No data are available in children aged < 6 months.

Adult population
No clinical study data are available in patients aged 18 years and older.

Method of administration

For intrathecal use. Treatment should be administered intrathecally using a lumbar puncture by healthcare professionals experienced in performing lumbar punctures.

- Immediately prior to dosing, draw the content from the vial into the syringe, remove air from the syringe, confirm the dose volume of 3 mL in the syringe, cap the syringe and deliver to the patient injection location.
- If indicated by the patient's clinical status, sedation should be considered.
- Imaging techniques to guide intrathecal injection may be considered.
- The patient should be evaluated prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture, to avoid serious procedural complications.
- Prior to administration, remove 3 mL of cerebrospinal fluid (CSF) using a lumbar puncture needle.
- Itvisma is administered as a single-dose bolus intrathecal injection over approximately 1 to 2 minutes.
- Following intrathecal injection, placement in Trendelenburg position (depending on the patient's clinical status) is recommended.

For detailed instructions on the preparation, handling, accidental exposure and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Reasons to postpone treatment

Due to the risk of serious immune response, it is recommended that patients are clinically stable in their overall health status (e.g. hydration and nutritional status, absence of infection, respiratory status) prior to injection. Itvisma should be postponed in patients with infection, either acute (e.g. respiratory) or chronic uncontrolled, until the infection has resolved and the patient is clinically stable. Clinical signs or symptoms of infection should not be evident at the time of injection.

Pre-existing immunity against AAV9

In Itvisma clinical studies, patients were required to have baseline serum anti-AAV9 antibody titres ≤ 1:50. The safety and efficacy of Itvisma in patients with elevated anti-AAV9 antibody titres have not been evaluated in humans.

Hepatotoxicity

Hepatotoxicity, which generally manifested as elevated ALT and/or AST levels, has occurred with onasemnogene abeparvovec intrathecal injection (see section 4.8). In order to mitigate potential aminotransferase elevations, a systemic corticosteroid should be administered to all patients before and after intrathecal injection. Immune-mediated hepatotoxicity may require adjustment of the immunomodulatory regimen including longer duration, increased dose, or prolongation of the corticosteroid taper (see section 4.2).

Patients with pre-existing hepatic impairment or acute hepatic viral infection may be at higher risk of liver injury. Patients with elevated liver function tests have not been studied in clinical studies with onasemnogene abeparvovec intrathecal injection.

Prior to onasemnogene abeparvovec intrathecal injection, liver function of all patients should be assessed by clinical examination and laboratory testing. Liver function should be monitored for at least 3 months after onasemnogene abeparvovec intrathecal injection administration, and at other times as clinically indicated. AST, ALT and total bilirubin should be assessed weekly for the first month after onasemnogene abeparvovec intrathecal injection administration and during the corticosteroid taper period. If the patient is clinically stable with unremarkable findings at the end of the corticosteroid taper period, liver function should continue to be monitored every two weeks for another month. Tapering of systemic corticosteroids should not be considered until AST/ALT levels are less than 2 × ULN (see section 4.2).

Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly clinically assessed and monitored closely. In case hepatic injury is suspected, further testing is recommended (e.g. albumin, prothrombin time, PTT and INR). Prompt consultation with a gastroenterologist or hepatologist is recommended, as necessary.

Thrombocytopenia

Transient decreases in platelet counts were typically observed within the first week after onasemnogene abeparvovec intrathecal injection administration. In most cases, platelet counts were $> 75 \times 10^9$/L and returned to baseline two weeks following onasemnogene abeparvovec intrathecal injection.

Platelet counts should be obtained before onasemnogene abeparvovec intrathecal 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.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) may occur. TMA is characterised by thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury. Concurrent immune system activation (e.g. infections, vaccinations) may be a contributing factor.

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

Thrombocytopenia is a key feature of TMA, therefore platelet counts should be monitored on a regular basis following onasemnogene abeparvovec intrathecal injection, as well as signs and symptoms of TMA, such as hypertension, bruising easily, seizures or decreased urine output. In case these signs and symptoms occur in the presence of thrombocytopenia, further diagnostic evaluation for haemolytic anaemia and renal dysfunction should be promptly undertaken. If clinical signs, symptoms and/or laboratory findings consistent with TMA occur, a haematologist and/or nephrologist should be consulted immediately to manage TMA as clinically indicated. Patients and caregivers should be informed about signs and symptoms of TMA and should be advised to seek urgent medical care if such symptoms occur.

Peripheral sensory neuropathy

Peripheral sensory neuropathy has occurred with onasemnogene abeparvovec intrathecal injection. Administration of onasemnogene abeparvovec intrathecal injection may result in sensory symptoms (e.g. numbness, tingling, prickling or pain in the arms, hands, legs and/or feet), with onset seen at approximately three weeks post-injection in clinical studies. Symptoms requiring management with additional therapies may persist, but can also gradually improve over time (see section 4.8). Sensory symptoms suggestive of peripheral sensory neuropathy may also occur as part of the natural course of SMA.

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

Risk of tumourigenicity as a result of vector integration

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

Onasemnogene abeparvovec intrathecal injection is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Random integration of recombinant AAV-vector DNA into human DNA has been reported with AAV gene therapies. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumourigenicity.

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

Blood, organ, tissue and cell donation

Patients treated with onasemnogene abeparvovec intrathecal injection should not donate blood, organs, tissues or cells for transplantation.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 3 mL dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vaccinations

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of onasemnogene abeparvovec in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). It is not known whether onasemnogene abeparvovec has the potential to be transferred to the foetus in humans. Therefore, women who are pregnant or may become pregnant should only be treated with Itvisma after a thorough benefit-risk evaluation.

Breast-feeding

There is no information available on the presence of onasemnogene abeparvovec in human milk, the effects on the breast-fed infant or the effects on milk production. A decision must be made whether to discontinue breast-feeding, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of onasemnogene abeparvovec on human fertility. In animal fertility studies, onasemnogene abeparvovec did not impact fertility in male or female mice at doses up to 1.1×10^{14} vg/kg administered intravenously (see section 5.3).

4.7 Effects on ability to drive and use machines

Onasemnogene abeparvovec intrathecal injection may have a minor influence on the ability to drive and use machines. Patients experiencing dizziness (see section 4.8) should avoid driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section are from 127 patients from studies COAV101B12301, COAV101B12302 and COAV101A12102 over a 52-week follow-up period (see section 5.1). The most frequently reported adverse reactions following Itvisma administration were upper respiratory tract infection (41.7%), pyrexia (36.2%), vomiting (28.3%), headache (13.4%), and increased hepatic enzyme (9.4%). The most frequently reported serious adverse reactions were vomiting (2.4%), increased hepatic enzyme (1.6%), headache (1.6%) and pyrexia (1.6%). The adverse reactions reported were similar across studies.

Tabulated list of adverse reactions

The adverse reactions identified with Itvisma in patients treated with intrathecal injection at the recommended dose are presented in Table 2. Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Tabulated list of adverse reactions to Itvisma

Adverse reactions by MedDRA SOC/PT and frequency	
Infections and infestations	
Very common	Upper respiratory tract infection[a)]
Blood and lymphatic system disorders	
Common	Thrombocytopenia[b)]
Nervous system disorders	
Very common	Headache[c)]
Common	Dizziness[c)]
Common	Peripheral sensory neuropathy[d)]
Common	Hypoaesthesia
Common	Paraesthesia
Gastrointestinal disorders	
Very common	Vomiting
Hepatobiliary disorders	
Common	Hepatic enzyme increased[e)]
General disorders and administration site conditions	
Very common	Pyrexia

a) Upper respiratory tract infection includes upper respiratory tract infection, viral upper respiratory tract infection, rhinitis, and oropharyngeal pain.
b) Thrombocytopenia includes thrombocytopenia and platelet count decreased.
c) Adverse reactions considered related to the lumbar puncture procedure.
d) Peripheral sensory neuropathy includes peripheral sensory neuropathy and neuropathy peripheral.
e) Hepatic enzyme increased includes hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatitis, hypertransaminasaemia and hepatic function abnormal.

Description of selected adverse reactions

Peripheral sensory neuropathy
In clinical studies, cases of peripheral sensory neuropathy (1.6%) have been observed within approximately three weeks following Itvisma administration. Patients presented with hypoaesthesia and paraesthesia. These cases required prolonged symptom management and some symptoms had not fully resolved at the end of the study (see section 4.4).

Hepatic laboratory abnormalities
In clinical studies, all patients received prophylaxis with corticosteroids. The majority of patients received the recommended immunomodulatory regimen with a median duration of approximately 60 days (see section 4.2). AST or ALT elevations > 3 × ULN were observed in 4.7% of patients following Itvisma administration. Serum transaminase elevations resolved with prednisolone treatment and patients recovered without clinical sequelae.

Immunogenicity
In the clinical studies COAV101B12301 and COAV101B12302, following a one-time Itvisma injection, increases from baseline in serum anti-AAV9 antibody titres occurred in all patients. Median serum anti-AAV9 antibody titres at 12 months following Itvisma injection were > 1:800 000 in both studies. No clear association between post-administration anti-AAV9 antibody level and safety findings or loss of efficacy was seen in the studied population over the follow-up period of 12 months post-dose.

During the 12-month period following Itvisma injection in studies COAV101B12301 and COAV101B12302, positive anti-SMN antibodies were observed in 5/75 (6.7%) and 2/27 (7.4%) Itvisma-treated patients, respectively. No clear association can be made between a positive anti-SMN antibody response and safety or efficacy of Itvisma over the follow-up period of 12 months post-dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Itvisma. The dose of Itvisma is a single, fixed dose and is administered only once, therefore overdose is considered unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilises AAV9 capsid to deliver a stable, fully functional human SMN transgene. The *SMN1* gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in the nucleus of transduced cells and is stably expressed in post-mitotic cells. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken-β-actin-hybrid), which results in continuous and sustained SMN expression. Proof of the mechanism of action mainly derives from non-clinical studies.

Clinical efficacy and safety

COAV101B12301 (STEER) phase III study in patients with SMA
This is a 52-week, randomised, double-blind, sham-controlled, multicentre study.

Efficacy was assessed in 126 patients with SMA aged 2 to < 18 years who were treatment-naïve and able to sit but never able to walk independently. Patients were randomised 3:2 and received Itvisma (1.2×10^{14} vg) by lumbar intrathecal injection (n=75) or sham procedure (n=51). Randomisation was stratified by age and pre-treatment Hammersmith Functional Motor Scale – Expanded (HFMSE) score at screening. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titre were excluded.

The primary endpoint was the change from baseline in HFMSE total score at the end of follow-up, defined as the average of the week 48 and week 52 assessment, in the overall study population (2 to < 18 years age group) with Itvisma compared to sham. A secondary endpoint was the proportion of patients with at least a 3-point improvement from baseline in HFMSE total score at the end of follow-up. The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising 33 graded items assessing movements ranging from sitting to using the stairs. Each item is scored from 0 to 2, with a maximum total score of 66. Higher scores indicate better motor function. Another secondary endpoint was the change from baseline in Revised Upper Limb Module (RULM) at the end of follow-up. The RULM is a SMA-specific assessment used to assess upper limb (proximal and distal) motor function. The RULM contains 19 graded items (18 scored from 0 to 2 and 1 scored from 0 to 1), and there is a maximum achievable score of 37, with higher scores indicating greater motor function.

The median age at screening was 4.54 years (range: 2.0 to 16.5 years) and the median reported age of onset of clinical signs and symptoms of SMA was 11 months (range: 6 to 33 months). Patients' highest motor milestone ever achieved included sitting, standing with or without support, or walking with support. At baseline, the mean HFMSE score was 17.97 and 18.17 in the Itvisma-treated group and sham-control group, respectively. The mean baseline RULM score was 16.52 in the Itvisma-treated group and 17.42 in the sham-control group. The baseline demographic characteristics were balanced between the Itvisma and sham arms.

The primary endpoint analysis showed a statistically significant and clinically meaningful improvement in HFMSE scores from baseline at the end of follow-up in the Itvisma-treated group compared to the sham-control group (Table 3 and Figure 1).

Table 3 Primary endpoint in study COAV101B12301

Endpoint	Itvisma-treated patients (N=75)	Sham-control patients (N=51)
Mean HFMSE total score at baseline (SD)	17.97 (10.110)	18.17 (9.756)
Mean HFMSE total score at the end of follow-up[1] (SD)	20.49 (11.356)	19.05 (10.132)
Change from baseline in total HFMSE score[2] at the end of follow-up in the overall study population (2 to < 18 years age group)[1, 2, 3, 4]	2.39 (0.439)	0.51 (0.532)
Difference from sham Estimate (95% CI)	1.88 (0.51 – 3.25)	

SD = Standard deviation

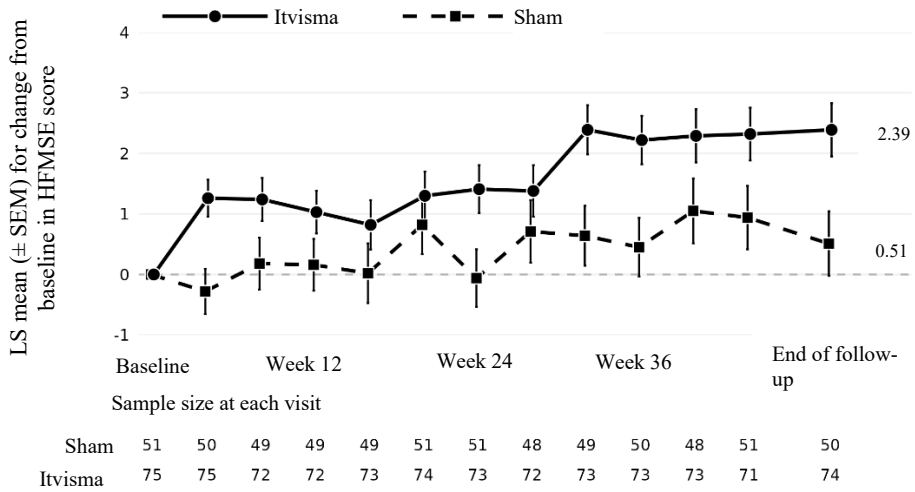
[1] The end of follow-up was defined as the average of the week 48 and week 52 assessment.

[2] Assessed using the Full Analysis Set (FAS) population, which included all participants who were dosed with Itvisma or who underwent sham procedure

[3] Least squares (LS) mean (standard error of the mean [SEM])

[4] The Mixed Model Repeated Measure (MMRM) analysis with fixed effects included treatment, scheduled visit, treatment by visit interaction, the strata, and the baseline HFMSE total score as covariate.

Figure 1 Change from baseline in HFMSE for patients aged 2 to < 18 years in study COAV101B12301



Note: Data represent LS mean ± SEM; intermediate time points are descriptive only and not controlled for multiplicity.

The change from baseline in RULM at the end of follow-up was assessed in the Itvisma-treated and sham-control groups. The least squares (LS) mean increase in RULM total score from baseline to the end of follow-up was 2.44 points in the Itvisma-treated group, and 0.92 points in the sham-control group. The treatment difference of 1.52 points in favour of the Itvisma-treated group did not meet statistical significance (95% CI: 0.34, 2.71) under an alpha level of 0.0025 per the pre-planned multiple testing strategy.

The percentage of patients with at least a 3-point improvement in total HFMSE score from baseline to the end of follow-up was numerically higher in the Itvisma-treated group (39.2%) than the sham-control group (26.0%), although the difference did not meet statistical significance (odds ratio (OR): 2.03; 95% CI: 0.9, 4.57).

Sixty-seven of the 75 patients from COAV101B12301 who received Itvisma continued to be followed for an additional 3 months after the end of follow-up. Over the combined follow-up period of up to 15 months following Itvisma administration, mean HFMSE scores continued to increase, demonstrating improved and sustained motor function.

COAV101B12302 (STRENGTH) phase III study in SMA patients previously treated with other SMA-modifying therapies

This is a phase III, open-label, single-arm, multicentre study of intrathecal administration of Itvisma (1.2×10^{14} vg) in 27 patients with SMA aged 2 to < 18 years (median age at screening: 7.0 years; range: 2.3 to 17.6 years) who discontinued previous SMA treatment (nusinersen n=21, risdiplam n=4, nusinersen and risdiplam [not concurrently] n=2). Prior to treatment with Itvisma, patients had previously received nusinersen for a mean duration of 4.3 years (range: 1.86 to 6.18 years), and risdiplam for a mean duration of 3.0 years (range: 0.39 to 6.28 years). All patients were able to sit but never able to walk independently. Patients' baseline motor function included sitting, standing with or without support and/or walking with support. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titre were excluded.

At week 52, patients showed overall stabilisation in motor function as measured by HFMSE (n=21), with a mean (SD) change from baseline of 0.17 (2.88), and RULM (n=21), with a mean (SD) change from baseline of 0.29 (2.85). After adjusting for baseline age stratum, the adjusted mean (LS mean) change from baseline to week 52 in HFMSE and RULM total score was 1.05 and 0.59, respectively. The majority of patients demonstrated maintenance of baseline motor milestones or higher motor milestones at week 52.

COAV101A12102 (STRONG) phase I/II study in patients with SMA

This is a phase I/II, open-label study in which Itvisma (1.2×10^{14} vg) was administered as a single intrathecal injection in 25 patients from 6 months to < 5 years of age at the time of dosing. All patients were treatment-naive and able to sit but never able to stand or walk independently at baseline. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titre were excluded. Patients were stratified in two groups based on age at dosing (6 months to < 2 years of age (N=13); 2 to < 5 years of age (N=12)). The median age at dosing was 17.7 months (range: 7 to 23 months) in the 6 months to < 2 years age group, and 33.7 months (range: 26 to 55 months) in the 2 to < 5 years age group. The median age of onset of clinical signs and symptoms of SMA was 8.0 months and 8.5 months in the 6 months to < 2 years group and 2 to < 5 years group, respectively.

The primary efficacy endpoint for patients 2 to < 5 years of age was the change from baseline in HFMSE at 12 months following Itvisma injection. The mean HFMSE score (SD) was 14.8 (9.98) at baseline and 21.3 (11.94) at month 12. The primary analysis in this age group showed LS mean change (95% CI) in HFMSE from baseline to month 12 of 6.0 (3.7, 8.3) points.

The primary efficacy endpoint for patients 6 months to < 2 years of age was the ability to stand alone for at least 3 seconds (Bayley Scales of Infant and Toddler Development (Bayley-III) – Gross Motor (GM) Subtest Item #40), at any post-baseline visit up to 12 months following Itvisma injection. The primary endpoint was not met; 1 of the 13 patients demonstrated this milestone at month 12.

Exploratory analyses in patients 6 months to < 2 years of age show improvements from baseline in gross and fine motor skills, as measured by the Bayley-III Gross and Fine Motor Subtests. All 13 patients showed improvement from baseline up to month 12 in gross and/or fine motor subtest total scores, with a mean change (SD) from baseline of 6.7 (6.46) and 12.7 (3.71), respectively. Furthermore, in a subset of patients who reached 2 years of age during the study and had at least seven months post-baseline HFMSE data (n=6), all patients showed increases in HFMSE score ranging from 1 to 14 points (mean ± SD change: 6.7 ± 4.72) from initial assessment of HFMSE to the end of month 7. Efficacy has not been established in the 6 months to < 2 years age-group.

Twelve of the 25 patients from COAV101A12102 were enrolled in a long-term study for up to 7.2 years. As of 30 June 2025, the majority of patients maintained or further improved their motor function. Nine of the 12 patients received concomitant nusinersen or risdiplam treatment at some point during the long-term study. The reason for concomitant nusinersen or risdiplam is unknown and a conclusion on the treatment effect in those patients cannot be made.

5.2 Pharmacokinetic properties

Onasemnogene abeparvovec vector shedding studies, which assess the amount of vector DNA eliminated from the body through saliva, urine, faeces and nasal secretions, were performed following intrathecal administration.

Vector DNA was detectable in shedding samples following intrathecal injection of onasemnogene abeparvovec. Shedding (excretion) of onasemnogene abeparvovec was primarily via faeces. The majority of the vector DNA (> 90%) is excreted within 2 weeks after dose administration. Peak shedding in faeces was estimated to be between 0.005% to 0.03% of total dose. The maximal shedding concentration in faeces was ~70-fold lower following intrathecal administration of 1.2×10^{14} vg in COAV101B12301 compared with intravenous administration of 1.1×10^{14} vg/kg (studies AVXS-101-CL-302 and AVXS-101-CL-303).

In subjects aged 6 months to < 2 years, the CSF volume increases between 1.0- to 1.6-fold. Based on this, onasemnogene abeparvovec exposure in the CSF in paediatric patients aged 6 months to < 2 years may be up to 1.6-fold higher compared to patients aged ≥ 2 years.

5.3 Preclinical safety data

Biodistribution

Following intrathecal administration in non-human primates, the vector was widely distributed with subsequent expression of transgene mRNA. The highest vector DNA concentration was detected in the liver, followed by the dorsal root ganglia (DRG) and spinal cord, with the lowest concentration in the gonads. The highest concentration of transgene mRNA tended to occur in the heart, liver and muscle.

In mice dosed with onasemnogene abeparvovec via intravenous or intracerebroventricular administration at PND1 (post-natal day 1), the viral vector was not detected in germline cells of males and females at week 3, 8 or 24 post-dosing. In juvenile non-human primates treated with a scAAV9 viral vector, which is utilised in onasemnogene abeparvovec but here carrying green fluorescent protein (GFP) or mCherry as transgene, this was shown to transduce oocytes of cycling females 13-17 months of age, but not the seminiferous tubules or germ cells in sexually mature males, following intrathecal, intracisterna magna and intravenous administration.

In non-human primates, high pre-existing serum anti-AAV9 antibody titres (corresponding to human titre values of up to approximately 1:25 000) were not shown to affect scAAV9 vector (utilised in onasemnogene abeparvovec) DNA distribution in the spinal cord following intrathecal administration.

General toxicity

In a 12-month toxicity study conducted in juvenile non-human primates, intrathecal administration of a single dose of onasemnogene abeparvovec at doses of 1.20×10^{13}, 3.0×10^{13}, or 6.0×10^{13} vg/animal, resulted at 6 weeks post-dosing in acute, minimal to moderate mononuclear cell inflammation and neuronal degeneration in the dorsal root ganglia (DRG) and trigeminal ganglia (TG), as well as axonal degeneration and/or gliosis in the spinal cord. At 12 months, these non-progressive findings resulted in partial to full resolution. These findings in non-human primates had no correlative clinical observations, therefore the clinical relevance in humans is unknown. Liver findings in juvenile non-human primates, including elevated transaminase levels and single-cell necrosis of hepatocytes, demonstrated complete reversibility at 12 months. A NOAEL (no observed adverse effect level) could not be identified because of the inflammation and degeneration in the CNS/DRG/TG already at the lowest dose.

Genotoxicity and carcinogenicity

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

Reproductive and developmental toxicity

In fertility and early embryonic development (FEED) studies conducted in mice, no adverse effects on male or female fertility were observed with onasemnogene abeparvovec at doses of 1.1×10^{13} or 1.1×10^{14} vg/kg administered intravenously.

In an embryofoetal development (EFD) study in mice, pregnant animals received an intravenous dose of either 1.1×10^{13} vg/kg or 1.1×10^{14} vg/kg of onasemnogene abeparvovec on GD6 (gestational day 6). There was no evidence of maternal toxicity, embryofoetal toxicity, teratogenicity or reduced viability. There was no onasemnogene abeparvovec DNA detected in any foetal tissue at GD18, despite the presence of vector DNA in the placenta, ovaries and uterus.

The NOAEL for the EFD study and FEED studies is 1.1×10^{14} vg/kg, corresponding to at least 7 times the recommended clinical intrathecal dose based on body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tromethamine
Magnesium chloride
Sodium chloride
Poloxamer 188
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

Contact of the medicinal product with medical devices made of polyvinylchloride (PVC), bisphenol-A (BPA), bis(2-ethylhexyl) phthalate (DEHP) or latex must be avoided.

6.3 Shelf life

2 years

After thawing

Once thawed, the medicinal product should not be re-frozen.
May be stored refrigerated at 2 °C to 8 °C in the original carton for 14 days. The date of receipt should be marked on the original carton before the medicinal product is stored in the refrigerator.

Once the dose is drawn into the syringe, it may be held at 2 °C to 8 °C for up to 24 hours, including a 5-hour maximum time out-of-refrigeration allowance within the 24-hour period. The vector-containing syringe should be discarded if not used within this time period.

6.4 Special precautions for storage

Store and transport frozen (≤ -60 °C).
Store in a refrigerator (2 °C – 8 °C) immediately upon receipt.
Store in the original carton.
For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Itvisma is supplied in a single-dose clear vial (5 mL cyclic olefin polymer) with stopper (20 mm chlorobutyl rubber) and seal (aluminium, flip-off) with a coloured cap (plastic). Each vial has a fill volume of 3 mL.

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Thawing

- Thaw Itvisma in the refrigerator (2 °C to 8 °C) for approximately 4 hours, or at room temperature (20 °C to 25 °C) for approximately 1 hour.
- Prior to intrathecal injection, Itvisma should be brought to room temperature.
- Itvisma is a clear to slightly opaque, colourless to faint white solution. Do not use this medicinal product if you notice any particles, cloudiness, or discolouration once the frozen product has thawed and prior to administration.
- Do not shake.
- Once thawed, the medicinal product should not be re-frozen.
- After thawing, Itvisma should be given as soon as possible. Once the dose volume is drawn into the syringe it may be held in the refrigerator (2 °C to 8 °C) for up to 24 hours, including a 5-hour maximum time out-of-refrigeration allowance within the 24-hour period. Discard the vector-containing syringe if not used within this time period.

Precautions to be taken before handling or administering the medicinal product

- Itvisma should be handled aseptically under sterile conditions.
- This medicinal product contains genetically modified organisms (GMOs).
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering Itvisma.
- The vial must be thawed before use. Do not use Itvisma unless thawed.
- Immediately prior to dosing, draw the content from the vial into the syringe, remove air from the syringe, confirm the dose volume of 3 mL in the syringe, cap the syringe and deliver to the patient injection location.
- When assembling the injection, it must be ensured that the components' surface in contact with Itvisma solution consists of the compatible materials listed in Table 4. Device components must be indicated for intrathecal or neuraxial use.

Table 4 Component materials compatible with Itvisma

Component	Material of construction
18 to 19 G needle for withdrawal, maximum 40 mm long	Stainless steel
5 to 10 mL syringe[a]	Polypropylene
Syringe cap[a]	Polypropylene, polyethylene or methacrylate-acrylonitrile-butadiene-styrene
22 to 27 G spinal needle, maximum 156 mm long	Stainless steel
[a] Not to be manufactured with polyvinylchloride (PVC), bisphenol-A (BPA), bis(2-ethylhexyl) phthalate (DEHP) or latex	

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

- All spills of Itvisma must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean up materials must be double bagged and disposed of in accordance with local guidelines for handling of biological waste.
- Any unused medicinal product or waste material should be disposed of in accordance with local guidelines on handling of biological waste.
- All materials that may have come in contact with Itvisma (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local guidelines on handling of biological waste.
- Accidental exposure to Itvisma must be avoided. In the event of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. In the event of accidental exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2038/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Novartis Gene Therapies, Inc.
2512 S. TriCenter Blvd
Durham
NC 27713
United States

Name and address of the manufacturer(s) responsible for batch release

Novartis Pharmaceutical Manufacturing GmbH
Biochemiestraße 10
6336 Langkampfen
Austria

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to use of Itvisma in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where Itvisma is marketed, healthcare professionals (HCP) who are expected to prescribe, dispense and administer Itvisma are provided with the following Healthcare Professional Information Pack:
- SmPC
- Healthcare professional guide

The healthcare professional guide shall contain the following key messages:
- Before the start of treatment:
  - Evaluate the patient's vaccination schedule;
  - Inform the caregiver(s) about the main risks with Itvisma and their signs and symptoms, including hepatotoxicity, thrombocytopenia, peripheral sensory neuropathy and TMA; 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 Itvisma 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 Itvisma (e.g. resolution of infections) or if a postponement is warranted;
  - Check that corticosteroid treatment was started before administration of Itvisma.
- After treatment:
  - The corticosteroid treatment should continue for at least 2 months and not be tapered until AST/ALT are less than 2 × ULN, and all other assessments, e.g. total bilirubin, return to normal range;
  - Close and regular monitoring (clinical and laboratory) of the individual patient course should be performed for at least 3 months;
  - Prompt assessment of patients with worsening liver function tests and/or signs or symptoms of acute illness;
  - If patients do not respond adequately to corticosteroids, or if liver injury is suspected, HCP should consult a gastroenterologist or hepatologist;
  - If TMA is suspected, a haematologist and/or nephrologist should be consulted.
- 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.

The MAH shall ensure that in each Member State (MS) where Itvisma is marketed, all caregivers of patients in whom Itvisma treatment is planned or who have received Itvisma are provided with the following Patient Information Pack:

- Package Leaflet
- Patient/patient's caregiver information guide

The patient/patient's caregiver information guide shall contain the following key messages:

- What is SMA.
- What is Itvisma and how it works.
- Understanding the risks of Itvisma.
- Treatment with Itvisma: 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 Itvisma treatment, otherwise treatment may need to be postponed.
- Itvisma may increase the risk of abnormal clotting of blood in small blood vessels (thrombotic microangiopathy). 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. 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. Depending on the values and other signs and symptoms, further evaluations may be required.
- Itvisma can lower blood-platelet counts (thrombocytopenia). Cases generally occurred within the first week after the patient was given 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.
- Itvisma can lead to an increase in enzymes (proteins found within the body) produced by the liver. In some cases, Itvisma can affect the function of the liver and lead to injury of the liver. 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.
- 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.
- 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 Itvisma 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 Itvisma as it may lead to medical complications that may require urgent medical attention.
- 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Itvisma 1.2×10^{14} vector genomes solution for injection
onasemnogene abeparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains onasemnogene abeparvovec with a nominal concentration of 4×10^{13} vector genomes.

3. LIST OF EXCIPIENTS

Also contains tromethamine, magnesium chloride, sodium chloride, poloxamer 188, hydrochloric acid and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial (3 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intrathecal use
Single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Must use within 14 days of receipt
Date of receipt:

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen at ≤ -60 °C.
Store in a refrigerator immediately upon receipt.
Store in the original carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified organisms.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of biological waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2038/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Itvisma 1.2×10^{14} vector genomes solution for injection
onasemnogene abeparvovec
Intrathecal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Itvisma 1.2 × 10^{14} vector genomes solution for injection
onasemnogene abeparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you or your child may get. See the end of section 4 for how to report side effects.

If you are the caregiver of a child who will receive Itvisma, note that when "you" appears in the package leaflet, it refers to the child except where it says otherwise.

Read all of this leaflet carefully before you are given this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Itvisma is and what it is used for

Itvisma is a type of medicine called a gene therapy and contains the active substance onasemnogene abeparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic defect. The gene is delivered into the cells where it is needed using a modified virus that does not cause disease in humans.

Itvisma is used to treat 5q spinal muscular atrophy (SMA), a rare, serious inherited disease. It is used in adults, adolescents and children aged 2 years and older with inherited mutations (changes) affecting a gene called *SMN1*.

SMA occurs when there is a missing or abnormal version of a gene needed to make an essential protein called survival motor neuron (SMN) protein. Lack of SMN protein causes nerves that control muscles (motor neurons) to die. This results in muscles becoming weak and wasting away, with eventual loss of movement.

The active substance in Itvisma, onasemnogene abeparvovec, works by supplying a fully functioning copy of the SMN gene, which then helps the body to produce enough SMN protein for survival and maintenance of motor neurons.

2. What you need to know before you are given Itvisma

Do NOT use Itvisma
- if you are allergic to onasemnogene abeparvovec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Your doctor will carry out a test to check for antibodies before treatment to help decide if this medicine is suitable for you.

Liver problems
Talk to your doctor or nurse before this medicine is given if you have had any liver problems. This medicine can lead to an increase in enzymes (proteins) made by the liver, which can be a sign of a problem with the liver, or injury to the liver. Tell your doctor straight away if you notice any symptoms suggestive of liver problems, including:
- vomiting;
- jaundice (yellowing of the skin or of the whites of the eyes), or;
- reduced alertness (see section 4 “Possible side effects”).

You will have a blood test to check how well the liver is working before starting treatment with Itvisma. You will be given a type of medicine called a corticosteroid (for example, prednisolone) to help manage any increase in liver enzymes that may develop after you are given Itvisma (see section 3 “How Itvisma is given”).

You will also have regular blood tests for at least 3 months after treatment to monitor for changes in how your liver is working. These tests will be done more often during the first few weeks after Itvisma administration and while you are on corticosteroid treatment, and less often afterwards, if your liver tests are at an acceptable level.

Regular blood tests
This medicine can lower blood platelet levels (thrombocytopenia). You need to look out for possible signs of a low blood platelet count after you are given Itvisma, such as abnormal bruising or bleeding (see section 4 “Possible side effects”). Most cases of low blood platelet levels occurred within the first week after the patient was given Itvisma.

Before starting treatment with Itvisma, you will have a blood test to check the amount of blood cells (including red blood cells and platelets) in your body. You will also have regular blood tests for a period of time after treatment to monitor for changes in platelets.

Nerve problems affecting sensation of pain, temperature and touch (peripheral sensory neuropathy)
Peripheral sensory neuropathy has occurred with Itvisma. Symptoms may occur approximately three weeks after Itvisma is given. Possible signs you need to look out for after you have been given this medicine include numbness, tingling, prickling or pain in the arms, hands, legs and/or feet. Tell your doctor straight away if you develop any of these signs.

Abnormal clotting of blood in small blood vessels (thrombotic microangiopathy)
Thrombotic microangiopathy may occur. Thrombotic microangiopathy is a serious condition where tiny blood clots form in the smallest blood vessels throughout the body. It is associated with thrombocytopenia, a decrease in blood platelets (components that help the blood to clot) and destruction of red blood cells. It can be life-threatening if not treated promptly. These blood clots could affect the kidneys. Your doctor may want to check your blood platelet levels and blood pressure. Before starting treatment with Itvisma, you will have a blood test to check your creatinine level, which is an indicator of how your kidneys are working. Possible signs you need to look out for after you have been given Itvisma include bruising easily, seizures (fits) or decrease in urine output. Seek urgent medical attention if you develop any of these signs.

Risk of tumours associated with potential insertion into the DNA
There is a possibility that gene therapies such as Itvisma can insert into the DNA of human body cells. As a consequence, Itvisma could contribute to a risk of tumours because of the nature of the medicine. You should discuss this with your doctor. In the event of a tumour, your doctor may take a sample for further evaluation.

Infections
An infection (e.g. cold, flu or bronchiolitis) before or after Itvisma treatment may lead to more serious complications. Caregivers and others with whom you are in close contact should follow infection prevention practices (e.g. hand hygiene, coughing/sneezing etiquette, limiting potential contacts). You need to look out for signs of an infection such as coughing, wheezing, sneezing, runny nose, sore throat or fever. Tell your doctor straight away if you notice any symptoms suggestive of infection **before** or **after** Itvisma treatment. If you have an infection before Itvisma treatment, your doctor may delay treatment until the infection has resolved.

Blood, organ, tissue and cell donation
After you have been treated with Itvisma, you will not be able to donate blood, organs, tissues or cells. This is because Itvisma is a gene therapy medicine.

Other medicines and Itvisma
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Vaccinations
As corticosteroids can affect the body's immune (defence) system, your doctor may decide to delay giving some vaccinations while you are receiving corticosteroid treatment (see section 3, "How Itvisma is given"). Talk to your doctor or nurse if you have any questions.

Pregnancy and breast-feeding
There is no information on the use of Itvisma in pregnant or breast-feeding women. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, talk to your doctor for advice before being treated with Itvisma.

Driving and using machines
Do not drive or use machines if you experience dizziness (see section 4 "Possible side effects"). Talk to your doctor first.

Itvisma contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 3 mL dose, that is to say essentially 'sodium-free'.

3. How Itvisma is given

The recommended dose of Itvisma is 1.2×10^{14} vector genomes (vg). Itvisma will be given to you ONCE only.

Itvisma will be given to you in a hospital setting under the supervision of a doctor experienced in the management of patients with SMA.

Itvisma is given by injection into the lower back. This injection, called a lumbar puncture, is done by inserting a needle into the space around the spinal cord. You may also be given a medicine to make you relax or sleep during the procedure. Care after you are given Itvisma will be provided by your doctor.

You will also be given prednisolone (or another corticosteroid) by mouth, starting 24 hours before being given Itvisma. The dose of corticosteroid will depend on your weight. Your doctor will work out the total dose to give.

You will be given corticosteroid treatment daily for about 2 months after the dose of Itvisma, or until your liver enzymes decrease to an acceptable level. The doctor will slowly reduce the dose of corticosteroid until treatment can be fully stopped. Tell your doctor if you vomit before or after you take the corticosteroid dose; your doctor can then make sure you are receiving the full dose.

If you have any further questions ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek urgent medical attention if you develop any of the following serious side effects:

Common (may affect up to 1 in 10 people)
- bruising or bleeding for longer than usual if you have been hurt – these may be signs of a low blood platelet count (thrombocytopenia)
- nerve problems affecting sensation of pain, temperature, touch (peripheral sensory neuropathy)
- sensations like numbness, tingling, pins and needles (paraesthesia)
- reduced sense of touch or sensation (hypoaesthesia)

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people)
- nose and throat (upper respiratory tract) infection
- fever
- vomiting
- headache

Common (may affect up to 1 in 10 people)
- increases in liver enzymes seen in blood tests
- dizziness

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How Itvisma is stored

Keep this medicine out of the sight and reach of children.

The following information is for healthcare professionals who will prepare and give the medicine.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

The vial will be transported frozen (at or below -60 °C).

Store in the original carton.

Upon receipt the vial should be refrigerated at 2 °C to 8 °C immediately, and in the original carton. Itvisma therapy should be initiated within 14 days of receipt of the vial.

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

Once the dose is drawn into the syringe, it may be held at 2 °C to 8 °C for up to 24 hours, including a 5-hour maximum time out-of-refrigeration allowance within the 24-hour period.

This medicine contains genetically-modified organisms. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of biological waste. As this medicine will be given by a doctor, the doctor is responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Itvisma contains
- The active substance is onasemnogene abeparvovec. Each vial contains 1.2×10^{14} vector genomes onasemnogene abeparvovec in 3 mL solution.
- The other ingredients are tromethamine, magnesium chloride, sodium chloride, poloxamer 188, hydrochloric acid (for pH adjustment) and water for injections (see also section 2 “Itvisma contains sodium”).

What Itvisma looks like and contents of the pack
Itvisma is a clear to slightly opaque, colourless to faint white solution for injection.

Itvisma is supplied in a carton of one vial containing a nominal fill volume of 3 mL. Each vial is for single use only.

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90443 Nuremberg
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using.

Each vial is for single use only.

Handling

- Itvisma should be handled aseptically under sterile conditions.
- Prior to intrathecal injection, Itvisma should be brought to room temperature. Thaw Itvisma in the refrigerator (2 °C to 8 °C) for approximately 4 hours, or at room temperature (20 °C to 25 °C) for approximately 1 hour.
- Itvisma is a clear to slightly opaque, colourless to faint white solution. Do not use this medicinal product if you notice any particles, cloudiness or discolouration once the frozen product has thawed and prior to administration.
- Do not shake.
- Once thawed, the medicinal product should not be re-frozen.
- After thawing, Itvisma should be given as soon as possible. Once the dose volume is drawn into the syringe it may be held in the refrigerator (2 °C to 8 °C) for up to 24 hours, including a 5-hour maximum time out-of-refrigeration allowance within the 24-hour period. Discard the vector-containing syringe if not used within this time period.

Preparation

- This medicinal product contains genetically modified organisms (GMOs).
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering Itvisma.
- When assembling the injection, it must be ensured that the components' surface in contact with Itvisma solution consists of the compatible materials listed in the table below. Device components must be indicated for intrathecal or neuraxial use.

Component materials compatible with Itvisma

Component	**Material of construction**
18 to 19 G needle for withdrawal, maximum 40 mm long	Stainless steel
5 to 10 mL syringe[a]	Polypropylene
Syringe cap[a]	Polypropylene, polyethylene or methacrylate-acrylonitrile-butadiene-styrene
22 to 27 G spinal needle, maximum 156 mm long	Stainless steel
[a] Not to be manufactured with polyvinylchloride (PVC), bisphenol-A (BPA), bis(2-ethylhexyl) phthalate (DEHP) or latex	

Administration

For intrathecal use. Treatment should be administered intrathecally using a lumbar puncture by healthcare professionals experienced in performing lumbar punctures.

- Immediately prior to dosing, draw the content from the vial into the syringe, remove air from the syringe, confirm the dose volume of 3 mL in the syringe, cap the syringe and deliver to the patient injection location.
- If indicated by the patient's clinical status, sedation should be considered.
- Imaging techniques to guide intrathecal injection may be considered.
- The patient should be evaluated prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture, to avoid serious procedural complications.
- Prior to administration, remove 3 mL of cerebrospinal fluid (CSF) using a lumbar puncture needle.

- Itvisma is administered as a single-dose bolus intrathecal injection over approximately 1 to 2 minutes.
- Following intrathecal injection, placement in Trendelenburg position (depending on the patient's clinical status) is recommended.

Accidental exposure
Accidental exposure to Itvisma must be avoided.

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

All spills of Itvisma must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of in accordance with local guidelines on handling of biological waste.

Disposal
All materials that may have come in contact with Itvisma (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local guidelines on handling of biological waste.