

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ITVISMA® (ONASEMNOGENE ABEPARVOVEC) SOLUTION FOR INTRATHECAL (IT) INJECTION

WARNING: HEPATOTOXICITY

- Acute serious liver injury and elevated aminotransferases can occur with ITVISMA. (see 4.4 Special warnings and precautions for use)
- Patients with pre-existing liver impairment may be at higher risk. (see 4.4 Special warnings and precautions for use)
- Prior to intrathecal injection, assess liver function by clinical examination and laboratory testing. Administer systemic corticosteroid before and after ITVISMA injection. Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated (see 4.2 Dose and method of administration, subheading Laboratory testing and monitoring to assess safety).

1 NAME OF THE MEDICINE

Onasemnogene abeparvovec

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 vector serotype 9 (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.

Each mL contains onasemnogene abeparvovec with a nominal concentration of 4×10^{13} vector genomes (vg). Vials will contain an extractable volume of not less than 3 mL. Each single-dose vial contains 1.2×10^{14} vg of onasemnogene abeparvovec in 3 mL of solution.

Excipient with known effect

For the full list of the excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for intrathecal injection.

When thawed, it is a clear to slightly opaque, colourless to faint white solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ITVISMA (onasemnogene abeparvovec) is indicated for the treatment of 5q spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene in patients 2 years of age and before reaching 19 years of age.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

For single-dose intrathecal injection only.

Treatment with ITVISMA should be supervised by a physician experienced in the management of patients with SMA.

ITVISMA should only be administered intrathecally using a lumbar puncture by, or under the direction of healthcare professionals experienced in performing lumbar punctures.

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

ITVISMA is for a single-dose intrathecal injection only. Because treatment persists in nondividing cells, patients previously treated with onasemnogene abeparvovec (by any route of administration, including Zolgensma or ITVISMA) should not be treated with ITVISMA (see 5.1 Pharmacodynamic Properties).

The recommended dose of ITVISMA is 1.2×10^{14} vg.

Laboratory Testing and Monitoring to Assess Safety

Prior to ITVISMA injection, the following laboratory tests should be conducted at baseline (see 4.4. Special warnings and precautions for use, subheadings Hepatotoxicity, Thrombocytopenia and Thrombotic Microangiopathy):

- AAV9 antibody testing
- Liver function (aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin)
- Creatinine
- Complete blood count (including haemoglobin and platelet count)

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 ITVISMA 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 ITVISMA injection.

Patients with ALT, AST or total bilirubin greater than 2 times ULN have not been studied in clinical trials with ITVISMA.

After ITVISMA injection the following tests should be conducted on a regular basis as described in section 4.4. Special warnings and precautions for use

- Liver function (AST, ALT and total bilirubin) weekly for the month after ITVISMA injection and then weekly 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.
- Platelet counts weekly for the first month and as clinically indicated until platelet counts return to baseline.

Systemic Corticosteroid Treatment Pre- and Post-ITVISMA injection

To dampen an immune response to ITVISMA, immunomodulation with corticosteroids is recommended. Elevations in liver aminotransferases or decreased platelet counts may occur following treatment (see 4.4. Special warnings and precautions for use and 4.8 Adverse Effects (Undesirable effects)).

Treatment with Systemic Corticosteroid Prior to ITVISMA Injection

One day prior to ITVISMA injection, pre-treat with oral prednisolone at a dose of 1 mg/kg/day (or equivalent if another corticosteroid is used).

Continued Treatment with Systemic Corticosteroid and Liver Function Monitoring Following ITVISMA Injection

- Prednisolone should be administered daily at 1 mg/kg/day (or equivalent if another corticosteroid is used) for 30 days following ITVISMA injection (including the day of ITVISMA administration).
 - At the end of the 30-day period of systemic corticosteroid treatment, check liver status clinically and by assessing ALT, AST and total bilirubin. Liver function should be monitored for at least 3 months following ITVISMA injection, and at other times as clinically indicated (see 4.4. Special warnings and precautions for use, subheading Hepatotoxicity).
 - Promptly assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness.
- For patients with unremarkable findings (normal clinical exam, total bilirubin, and ALT and AST levels below 2 × ULN): Taper the prednisolone (or equivalent if another corticosteroid is used) dose over the next 28 days. Systemic corticosteroids should not be stopped abruptly, rather tapered gradually (see 4.4. Special warnings and precautions for use, subheading Hepatotoxicity).

- If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 × ULN and all other assessments return to normal range, and then taper the corticosteroid dose over the next 28 days or longer if needed. Systemic corticosteroids should not be stopped abruptly, rather 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 corticosteroid regimen, including increased dose, longer duration or prolongation of corticosteroid taper, may be considered (see 4.4. Special warnings and precautions for use). If oral corticosteroid therapy is not tolerated or not effective, intravenous corticosteroids may be considered as clinically indicated.

Variance from these recommendations is at the discretion of the treating physician. If another corticosteroid is used by the physician in place of prednisolone, similar considerations and approach to taper the corticosteroid dose after 30 days following ITVISMMA injection should be taken as appropriate.

Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following ITVISMMA injection (see 4.5 Interactions with other medicines and other forms of interactions).

Requirements for a genetically-modified organism

ITVISMMA contains a genetically-modified organism. Follow local institutional guidelines for storage, handling, administration and disposal of medicinal products containing genetically-modified organisms.

- ITVISMMA should be handled aseptically under sterile conditions. The syringe should be prepared aseptically under sterile conditions.
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while preparing or administering onasemnogene abeparvovec. Personnel should not work with onasemnogene abeparvovec if skin is cut or scratched.
- All spills of onasemnogene abeparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean up materials must be double bagged and disposed of per institutional guidelines for biohazard waste.
- All materials that may have come in contact with onasemnogene abeparvovec (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local institutional biosafety guidelines.
- Take precautions to avoid accidental exposure to onasemnogene abeparvovec. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Method of administration

ITVISMA is for single-dose intrathecal injection only. ITVISMA is for single use in one patient only. Discard any residue in accordance with local institutional guidelines.

Preparation

Required supplies and materials

- Needle for withdrawal
- Syringe
- Syringe cap
- Spinal needle

The supplies and materials compatible with ITVISMA are listed in Table 2. Device components must be indicated for intrathecal or neuraxial use.

Table 2 Component materials compatible with ITVISMA

Component	Material of Construction
18G to 19G Needle for withdrawal, maximum 1.5 " (40 mm) long	Stainless steel
5 mL to 10 mL Syringe ^a	Polypropylene
Syringe cap ^a	Polypropylene or Polyethylene or Methacrylate-Acrylonitrile-Butadiene-Styrene
22G to 27G Spinal needle, maximum 6.1 " (156 mm) long	Stainless steel
^a Not to be manufactured with Polyvinylchloride (PVC), Bisphenol-A (BPA), Bis(2-ethylhexyl) phthalate (DEHP) or Latex	

ITVISMA Preparation

- ITVISMA should be prepared aseptically.
- 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.
- Do not use ITVISMA unless thawed.
- If thawed in the refrigerator, remove ITVISMA from refrigerator on day of dosing.
- Prior to intrathecal injection, ITVISMA should be brought to room temperature.
- When thawed, ITVISMA is a clear to slightly opaque, colourless to faint white liquid, free of particles. After withdrawal of ITVISMA from the vial, a visual inspection is required. DO NOT use if particulates, cloudiness, or discoloration are visible.
- DO NOT SHAKE.

- 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.
- Once 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. Discard the vector-containing syringe if not used within this time period, in accordance with local institutional biosafety guidelines.
- DO NOT REFREEZE.

Procedural Preparation Instructions

- Consider sedation if indicated by the patient's clinical status.
- Consider imaging techniques to guide intrathecal injection of ITVISMA.
- Evaluate patient prior to and after intrathecal injection for the presence of potential conditions related to lumbar puncture, to avoid serious procedural complications.

Intrathecal Injection Instructions

- Prior to administration, remove 3 mL of cerebrospinal fluid (CSF) using a lumbar puncture needle.
- Administer ITVISMA as an intrathecal bolus injection over approximately 1 to 2 minutes.
- Following injection, standard post-lumbar puncture care is recommended.

Special populations

Renal impairment

The safety and efficacy of ITVISMA have not been established in patients with renal impairment.

Hepatic impairment

ITVISMA has not been studied in patients with hepatic impairment (see 4.4 Special warnings and precautions for use).

Paediatric patients

No studies of ITVISMA have been performed in paediatric patients less than 6 months of age (see 5.1 Clinical Studies).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in 6.1 List of excipients). Patients previously treated with onasemnogene abeparvovec (by any route of administration including Zolgensma or ITVISMA) should not be treated with ITVISMA.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatotoxicity

Hepatotoxicity, which generally manifested as elevated ALT and/or AST levels, has occurred with ITVISMA (see 4.8 Adverse Effects (Undesirable effects)). In order to mitigate potential

aminotransferase elevations, a systemic corticosteroid should be administered to all patients before and after ITVISMA injection. Immune-mediated hepatotoxicity may require adjustment of the corticosteroid regimen including longer duration, increased dose, or prolongation of the corticosteroid taper (see 4.2 Dose and method of administration).

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 trials with ITVISMA.

Prior to ITVISMA injection, liver function of all patients should be assessed by clinical examination and laboratory testing. Continue to monitor liver function for at least 3 months after ITVISMA administration, and at other times as clinically indicated. AST, ALT and total bilirubin should be assessed weekly for one month after ITVISMA 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 $2 \times \text{ULN}$ (see 4.2 Dose and method of administration).

Promptly assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness. In case hepatic injury is suspected, further testing is recommended (e.g., albumin, prothrombin time, partial thromboplastin time (PTT) and international normalized ratio (INR)). Promptly consult with a gastroenterologist or hepatologist, as necessary.

Thrombocytopenia

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

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.

Peripheral sensory neuropathy

Peripheral sensory neuropathy has occurred with ITVISMA. Administration of ITVISMA 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 improve over time (see 4.8 Adverse effects (undesirable effects)). 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.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) may occur. Thrombotic microangiopathy is characterized by thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury. Concurrent immune system activation (e.g., infections, vaccinations) may be a contributing factor. No cases of TMA have been observed with intrathecal administration of ITVISMA in clinical trials.

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 ITVISMA injection (see sub-section Thrombocytopenia), 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 hematologist 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.

Theoretical risk of tumorigenicity as a result of vector integration

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

ITVISMA 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 tumorigenicity.

Use in hepatic impairment

ITVISMA has not been studied in patients with hepatic impairment. ITVISMA therapy should be carefully considered in patients with hepatic impairment.

Use in renal impairment

The safety and efficacy of ITVISMA have not been established in patients with renal impairment.

Use in the elderly

Not applicable to this medicine.

Paediatric use

No studies of ITVISMA have been performed in paediatric patients less than 6 months of age (see 5.1 Clinical Studies).

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Live vaccines, such as MMR and varicella, should not be administered to patients on an immunosuppressive corticosteroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent), because high doses of corticosteroids may reduce the immune response to these vaccines. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following ITVISMA injection (see 4.2 Dose and method of administration). Seasonal prophylaxis against respiratory syncytial virus (RSV) is recommended and should be up-to-date.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no data on the effect of ITVISMA on human fertility. In animal fertility studies, onasemnogene abeparvovec did not impact fertility in male or female mice with a single IV dose up to 1.1×10^{14} vg/kg when given several weeks prior to mating with untreated animals. However, oestrous cycling was prolonged in female mice at this dose.

Intrathecal or intra-cisterna magna administration of a related AAV9 construct to adult cynomolgus monkeys resulted in the detection of vector DNA in the oocytes and ovarian stromal cells of females administered 1×10^{13} and 3×10^{13} vg/animal at 28-days post-administration of the product. In mice, IV, or intracerebroventricular (ICV) administration of onasemnogene abeparvovec resulted in no detection of vector DNA in the germline cells of males and females at 24 weeks post-administration.

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to treatment with ITVISMA (see sub-section Use in Pregnancy).

Contraception

Females

Females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) and should refrain from egg donation for 6 months following ITVISMA administration.

Males

Males capable of fathering a child should use a barrier method of contraception and should refrain from sperm donation for 3 months following ITVISMA administration.

Use in pregnancy - B2

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. There are no available data from animal embryofetal development studies with onasemnogene abeparvovec. It is not known whether ITVISMA has the potential to be transferred to the fetus. Therefore, women who are pregnant or desire to become pregnant should only be treated with ITVISMA after a thorough benefit-risk evaluation.

Use in lactation

There is no information available on the presence of ITVISMA in human milk, the effects on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ITVISMA and any potential adverse effects on the breastfed child from ITVISMA or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Across all clinical studies, a total of 167 patients were treated with ITVISMA, with a median follow-up duration of 13.83 months (range: 0.2 to 74.5 months).

The safety data described in this section are from 127 treatment-naïve and treatment-experienced patients who received ITVISMA at the recommended dose (1.2×10^{14} vg) in a double-blind, sham-controlled study and 2 open-label studies. The patients ranged in age from 0.6 to 17.7 years at the time of administration. The duration of follow-up was 52 weeks.

Among these 127 patients, the most frequently ($\geq 5\%$) reported adverse reactions following ITVISMA administration were upper respiratory tract infection, pyrexia, vomiting, headache, hepatic enzyme increased, and pain in extremity. The adverse reactions reported in treatment-naïve patients treated with ITVISMA were similar to those in treatment-experienced patients.

Tabulated summary of adverse drug reactions from clinical trials

The adverse drug reactions identified with ITVISMA in patients treated with intrathecal injection at the recommended dose (1.2×10^{14} vg) in a double-blind, sham-controlled study and 2 open-label studies are presented in Table 3.

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 3 Adverse drug reactions following treatment with ITVISMA

Adverse Drug Reactions	Frequency, % (N=127)	Frequency Category
Infections and infestations		
Upper respiratory tract infection ^{a)}	41.7	Very common
Blood and lymphatic system disorders		
Thrombocytopenia ^{b)}	2.4	Common
Nervous system disorders		
Headache ^{c)}	13.4	Very common
Dizziness ^{c)}	3.9	Common
Peripheral sensory neuropathy ^{d)}	1.6	Common
Hypoaesthesia	1.6	Common
Paraesthesia	1.6	Common
Gastrointestinal disorders		
Vomiting	28.3	Very common
Musculoskeletal and connective tissue disorders		
Pain in extremity	7.9	Common
General disorders and administration site conditions		
Pyrexia	36.2	Very common
Investigations		
Hepatic enzyme increased ^{e)}	9.4	Common
^{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, hypertransaminaemia and hepatic function abnormal.		

Description of selected adverse drug reactions*Peripheral sensory neuropathy*

In clinical trials, cases of peripheral sensory neuropathy have been observed within approximately three weeks following ITVISMA administration. These cases required prolonged symptom management, with improvement followed by stabilization of symptoms.

Laboratory abnormalities

In clinical trials, AST or ALT elevations $> 3 \times \text{ULN}$ were observed in 4.7% of patients following ITVISMMA administration. Serum transaminase elevations resolved with prednisolone treatment and patients recovered without clinical sequelae. The majority of patients received the recommended corticosteroid regimen (median duration: approximately 60 days) (see 4.2 Dose and method of administration).

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <https://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

SMA is caused by a bi-allelic mutation in the SMN1 gene, which results in insufficient SMN protein expression. Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilises the AAV9 capsid to deliver a stable fully functional copy of the transgene encoding the human survival motor gene (SMN1) protein. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in humans and is expected to be stably expressed for an extended period of time in post-mitotic cells. Rare instances of random vector integration into human DNA are possible with recombinant AAV (see section 4.4 Special warnings and precautions for use). The AAV9 virus is not known to cause disease in humans.

Proof of the mechanism of action by the intrathecal route has been supported by nonclinical and clinical studies.

Pharmacodynamics (PD)

There are no clinically relevant pharmacodynamics data for onasemnogene abeparvovec.

Clinical trials

The efficacy of ITVISMMA in patients 6 months of age and older with SMA was evaluated in a

double-blind, sham-controlled clinical study (COAV101B12301) and 2 open-label clinical studies (COAV101B12302 and COAV101A12102).

COAV101B12301 (STEER) Phase 3 study in patients with SMA

COAV101B12301 is a Phase 3, multicentre study including:

- Period 1 (Week 1-52): a 52-week, randomized, double-blind, sham-controlled period.
- Period 2 (Week 53-64): a 12-week period that began following completion of Period 1. Eligible patients who received sham procedure during Period 1 were treated with ITVISMA, and eligible patients treated with ITVISMA during Period 1 received sham procedure.

Efficacy was assessed in 126 patients with SMA aged 2 to less than 18 years who were treatment-naïve, and 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 were randomized 3:2 and received ITVISMA (1.2×10^{14} vg) by lumbar intrathecal injection (n=75) or sham procedure (n=51). Randomization was stratified by age and pre-treatment Hammersmith Functional Motor Scale – Expanded (HFMSE) score at screening.

The primary endpoint was the change from baseline in HFMSE total score at the end of Period 1 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 Period 1. The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising of 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 Period 1. 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.

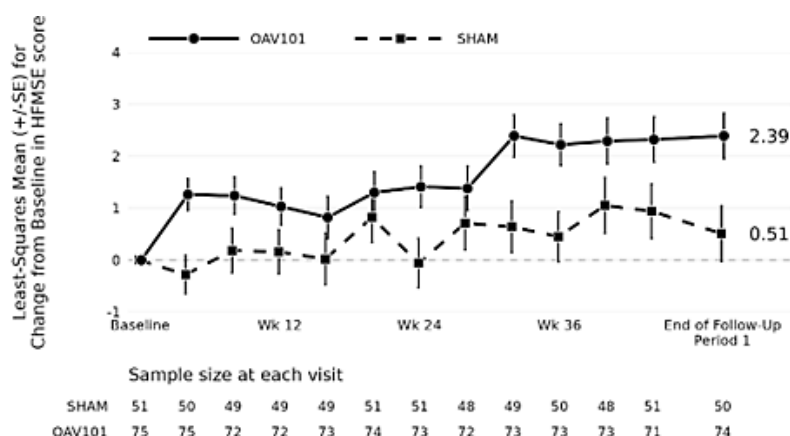
The median age at screening was 4.54 years (range: 2.0 to 16.5 years) and the median age of onset of clinical signs and symptoms of SMA was 11 months (range: 6 to 33 months). At baseline, the mean HFMSE score was 17.97 and 18.17 in the ITVISMA-treated group and sham-control group, respectively. The mean 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 analysis showed a statistically significant and clinically meaningful improvement in HFMSE scores from baseline at the end of Period 1 in the ITVISMA-treated group compared to the sham-control group (Table 4, Figure 1).

Table 4 Primary endpoint in Study COAV101B12301

Endpoint	ITVISMA- treated Patients (N=75)	Sham-control Patients (N=51)
Change from baseline in total HFMSE score ¹ at the end of Period 1 in the overall study population (2 to <18 years age group) ^{1, 2, 3}	2.39 (0.439)	0.51 (0.532)
Difference from sham Estimate (95% CI) p-value	1.88 (0.51 – 3.25) 0.0074	
¹ Assessed using the Full Analysis Set (FAS) population, which included all participants who were dosed with ITVISMA or who underwent sham procedure during Period 1 ² Least squares (LS) mean (standard error of the mean [SEM]) ³ 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 during Period 1 for patients aged 2 to <18 years in Study COAV101B12301

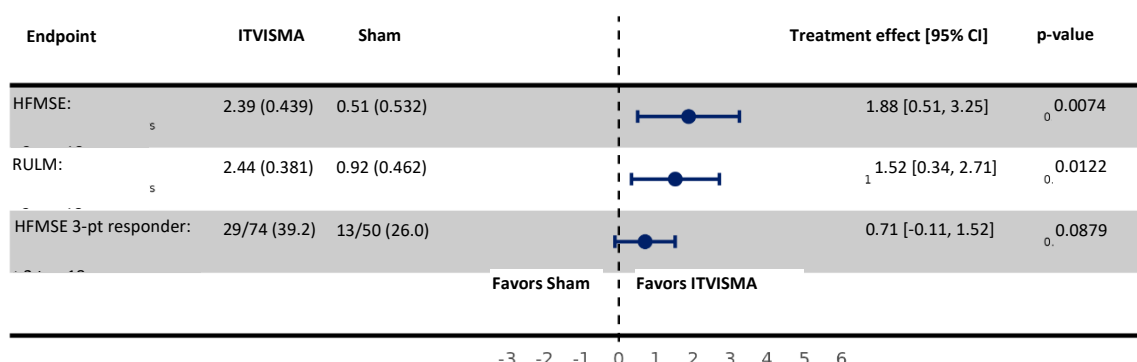


The change from baseline in RULM at the end of Period 1 was assessed in the ITVISMA-treated and sham-control groups. The least-squares (LS) mean increase in RULM total score from baseline to the end of Period 1 was 2.44 points in the ITVISMA-treated group, and 0.92 points in the sham-control group. The treatment difference of 1.52 points in favour of the ITVISMA-treated group did not meet statistical significance (95% CI: 0.34, 2.71; $p=0.0122$) 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 Period 1, was 39.2% in the ITVISMA-treated group and 26.0% in the sham-control group. This difference did not meet statistical significance (odds ratio (OR): 2.03; 95% CI: 0.9, 4.57; $p=0.0879$).

The results of the primary and secondary endpoints in the overall study population (2 to <18 years age group) are shown in Figure 2.

Figure 2 Primary and secondary endpoint results in Study COAV101B12301



Group estimates are displayed as LS-mean (SEM) for “Change from baseline” endpoints, and as n/m (%) for “Achievement of at least a 3-point improvement in HFMSE total score” endpoint, where n=number of patients achieving at least a 3-point improvement from baseline in HFMSE total score, and m= total number of patients at end of Period 1. Treatment effect is displayed as LS-mean [95% confidence interval] for “Change from baseline” endpoints, and as log (OR) [95% confidence interval] for “Achievement of at least a 3-point improvement in HFMSE total score” endpoint.

COAV101B12302 (STRENGTH) Phase 3 study in SMA patients previously treated with other SMA-modifying therapies

COAV101B12302 is a Phase 3, open-label, single-arm, multicenter study of intrathecal administration of ITVISM (1.2 x 10¹⁴ vg) in 27 patients with SMA aged 2 to less than 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 ITVISM, 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.

At Week 52, patients showed overall stabilization 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 1/2 study in patients with SMA

COAV101A12102 is a Phase 1/2, open-label study in which ITVISM (1.2 x 10¹⁴ 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-naïve and able to sit, but never able to stand or walk independently at baseline. 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 assessment of efficacy for patients 2 to <5 years of age was the change from baseline in HFMSE at 12 months following ITVISM injection. The primary analysis in this age group showed a LS mean change (95% CI) in HFMSE from baseline to Month 12 of 6.0 (3.7, 8.3) points.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics (PK)

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. The shedding observed in these studies does not indicate whether vector DNA was present in the capsid or whether intact vector was present.

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.

Immunogenicity

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

In the clinical studies COAV101B12301 and COAV101B12302, following a one-time ITVISMA injection, increases from baseline in anti-AAV9 antibody titres occurred in all patients. Median AAV9 antibody titres at 12 months following ITVISMA injection were $\geq 1:819,200$ in both studies.

In non-human primates, high pre-existing serum anti-AAV9 antibody titres (corresponding to estimated human titre values of up to approximately 1:25000) were not shown to affect scAAV9 vector (utilised in onasemnogene abeparvovec) DNA distribution in the spinal cord following intrathecal administration.

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%) of 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.

5.3 PRECLINICAL SAFETY DATA

Following intrathecal administration in non-human primates, the vector was widely distributed. The highest vector DNA concentration was detected in the liver, followed by the dorsal root ganglia (DRG) and spinal cord.

In a 12-month toxicity study conducted in juvenile non-human primates, intrathecal administration of a single dose of onasemnogene abeparvovec at doses of 1.2×10^{13} (equivalent to the clinical therapeutic dose), 3×10^{13} and 6×10^{13} vg/animal, resulted in acute, minimal to moderate mononuclear cell inflammation and neuronal degeneration in the 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.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of onasemnogene abeparvovec.

Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of onasemnogene abeparvovec (see section 4.4 Theoretical risk of tumorigenicity as a result of vector integration).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Trometamol, magnesium chloride hexahydrate, sodium chloride, poloxamer, hydrochloric acid (for pH adjustment) and water for injections.

Contains no preservative.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Preparation of pack contents is carried out aseptically under sterile conditions. To reduce microbiological hazard, use as soon as practicable after dispensing into the syringe. If storage is necessary, hold at room temperature (20°C – 25°C) for not more than 5 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

- ITVISMA is shipped and delivered frozen ($\leq -60^{\circ}\text{C}$) in a single-dose clear vial.
- Upon receipt, immediately place the carton in a refrigerator at 2°C to 8°C.
- ITVISMA is stable for 14 days from receipt when stored at 2°C to 8°C.
- DO NOT REFREEZE.
- Must use within 14 days of receipt.

After thawing, ITVISMA should be given as soon as possible. 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 maximum cumulative time out-of-refrigeration of 5 hours at room temperature within the 24-hour period. Discard the vector-containing syringe if not used within this time period, in accordance with local institutional biosafety guidelines.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

This medicine contains genetically modified organisms. Unused medicine and waste

products must be disposed of in compliance with the local institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS Number: 1922968-73-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 October 2026

10 DATE OF REVISION

NA

SUMMARY TABLE OF CHANGES

NA

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