NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
Zolgensma 2 x 10^13 vg/mL Suspension for Intravenous (MAL24026006AZ)

ACTIVE INGREDIENT:
Onasemnogene abeparvovec 2.0 x 10^{13} vector genomes (vg)/mL

PRODUCT REGISTRATION HOLDER:
Novartis Corporation (Malaysia) Sdn. Bhd.

PRODUCT MANUFACTURER:
Novartis Gene Therapies, Inc., Durham, US

APPROVAL DATE:
8 February 2024 (DCA 393)

1.0 BACKGROUND INFORMATION

- The DCA has registered **Spinraza** 12 mg Solution for Injection (MAL22086002ACRZ; nusinersen) and **Evrysdi** Powder for oral solution 0.75 mg/mL (MAL21086002ARZ; risdiplam) for the treatment of SMA. These two SMN2 splicing modulators require repeated, lifelong treatment for maintenance of effect and do not address the fundamental root cause of SMA.

- Zolgensma is a gene therapy treatment that provides a one-time therapy that directly targets the genetic root cause of the disease by delivering a functional copy of the human SMN gene. It is a non-replicating, recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the SMN gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter.

- The designation of Orphan Medicine for this product for Spinal muscular atrophy (G12.0) has been approved by Drug Evaluation Committee Meeting (date of designation: 16 Sept 2022).

1.1 Approved Indication

Zolgensma is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age:
- with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

1.2 Approved Posology

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 onasemnogene abeparvovec, baseline laboratory testing is required, including, but not limited to:
- AAV9 antibody testing using an appropriately validated assay,
- liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, partial thromboplastin time (PTT), and international normalised ratio (INR),
- creatinine,
- complete blood count (including haemoglobin and platelet count), and
- troponin-I.

The need for close monitoring of liver function, platelet count and troponin-I after administration and the need for corticosteroid treatment are to be considered when establishing the timing of onasemnogene abeparvovec treatment.
Due to the increased risk of serious systemic immune response, it is recommended that patients are clinically stable in their overall health status (e.g. hydration and nutritional status, absence of infection) prior to onasemnogene abeparvovec infusion. In case of acute or chronic uncontrolled active infections, treatment should be postponed until the infection has resolved and the patient is clinically stable

Posology
For single-dose intravenous infusion only.

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

Table 1 gives the recommended dosing for patients who weigh 2.6 kg to 21.0 kg.

Table 1: Recommended dosing based on patient body weight

Patient weight range (kg)	Dose (vg)	Dose volume[a] (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9.9×10^{14}	49.5
9.1 – 9.5	1.05×10^{14}	52.3
9.6 – 10.0	1.10×10^{14}	55.0
10.1 – 10.5	1.16×10^{14}	57.8
10.6 – 11.0	1.21×10^{14}	60.5
11.1 – 11.5	1.27×10^{14}	63.3
11.6 – 12.0	1.32×10^{14}	66.0
12.1 – 12.5	1.38×10^{14}	68.8
12.6 – 13.0	1.43×10^{14}	71.5

Patient weight range (kg)	Dose (vg)	Dose volume[a] (mL)
13.1 – 13.5	1.49×10^{14}	74.3
13.6 – 14.0	1.54×10^{14}	77.0
14.1 – 14.5	1.60×10^{14}	79.8
14.6 – 15.0	1.65×10^{14}	82.5
15.1 – 15.5	1.71×10^{14}	85.3
15.6 – 16.0	1.76×10^{14}	88.0
16.1 – 16.5	1.82×10^{14}	90.8
16.6 – 17.0	1.87×10^{14}	93.5
17.1 – 17.5	1.93×10^{14}	96.3
17.6 – 18.0	1.98×10^{14}	99.0
18.1 – 18.5	2.04×10^{14}	101.8
18.6 – 19.0	2.09×10^{14}	104.5
19.1 – 19.5	2.15×10^{14}	107.3
19.6 – 20.0	2.20×10^{14}	110.0
20.1 – 20.5	2.26×10^{14}	112.8
20.6 – 21.0	2.31×10^{14}	115.5

[a] NOTE: Number of vials per kit and required number of kits is weight-dependent. Dose volume is calculated using the upper limit of the patient weight range.

Immunomodulatory regimen

An immune response to the AAV9 capsid will occur after administration of onasemnogene abeparvovec. This can lead to elevations in liver aminotransferases, elevations of troponin I, or decreased platelet counts. To dampen the immune response immunomodulation with corticosteroids is recommended. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion.

Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for signs and symptoms of active infectious disease of any nature.

Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen following the schedule below (see Table 2). 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 paediatric gastroenterologist or hepatologist and adjustment to the recommended immunomodulatory regimen, including increased dose, longer duration or prolongation of corticosteroid taper, should be considered. If oral corticosteroid therapy is not tolerated intravenous corticosteroid may be considered as clinically indicated.

Table 2 Pre- and post-infusion immunomodulatory regimen

Pre-infusion	24 hours prior to onasemnogene abeparvovec	Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used)
Post-infusion	30 days (including the day of administration of onasemnogene abeparvovec)	Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used)
	Followed by 28 days: *For patients with unremarkable findings (normal clinical exam, 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. Tapering of prednisolone (or equivalent if another corticosteroid is used), e.g. 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day oral prednisolone Systemic corticosteroids (equivalent to oral prednisolone 1 mg/kg/day) Systemic corticosteroids should be tapered gradually.

Liver function (ALT, AST, total bilirubin) should be monitored at regular intervals for at least 3 months following onasemnogene abeparvovec infusion (weekly in the first month and during the entire corticosteroid taper period, followed by every two weeks for another month), and at other times as clinically indicated. Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly clinically assessed and monitored closely.

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

Special populations

Renal impairment

The safety and efficacy of onasemnogene abeparvovec have not been established in patients with renal impairment and onasemnogene abeparvovec therapy should be carefully considered. A dose adjustment should not be considered.

Hepatic impairment
Patients with ALT, AST, total bilirubin levels (except due to neonatal jaundice) >2 × ULN or positive serology for hepatitis B or hepatitis C have not been studied in clinical studies with onasemnogene abeparvovec. Onasemnogene abeparvovec therapy should be carefully considered in patients with hepatic impairment. A dose adjustment should not be considered.

0SMN1/1SMN2 genotype
No dose adjustment should be considered in patients with a bi-allelic mutation of the SMN1 gene and only one copy of SMN2.

Anti-AAV9 antibodies
No dose adjustment should be considered in patients with baseline anti-AAV9 antibody titres above 1:50.

Paediatric population
The safety and efficacy of onasemnogene abeparvovec in premature neonates before reaching full-term gestational age have not been established. No data are available. Administration of onasemnogene abeparvovec should be carefully considered because concomitant treatment with corticosteroids may adversely affect neurological development.

There is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established. Currently available data are described in section 5.1 (Pharmacodynamic properties). A dose adjustment should not be considered.

1.3 Method of administration

Intravenous Infusion

1.4 Pharmacological Aspects

Pharmacotherapeutic group: Musculo-skeletal system; Other drugs for disorders of the musculo-skeletal system (ATC Code: M09AX09)

Pharmacodynamic Properties:

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 the disease. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The ability of the AAV9 capsid to cross the blood brain barrier and transduce motor neurons has been demonstrated. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The AAV9 virus is not known to cause disease in humans. The transgene is introduced 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 protein expression. Proof of the mechanism of action has been supported by non-clinical studies and by human biodistribution data.

Pharmacokinetic Properties:

Onasemnogene abeparvovec vector shedding studies, which assess the amount of vector eliminated from the body through saliva, urine and faeces were performed.

Onasemnogene abeparvovec was detectable in shedding samples post-infusion. Clearance of onasemnogene abeparvovec was primarily via faeces and the majority is cleared within 30 days after dose administration.

Biodistribution was evaluated in 2 patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec at the dose of 1.1 x 10^{14} vg/kg. Both cases showed that the highest levels of vector DNA were found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph node, skeletal muscles, peripheral nerves, kidney, lung, intestines, gonads, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalized SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Drug Substance

Onasemnogene abeparvovec is a non-replicating, recombinant adeno-associated virus serotype 9 (AAV9) containing the human survival motor neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). One of the two adeno-associated vector (AAV) inverted terminal repeats (ITRs) has been modified to promote

intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.

Validation was performed on for three consecutive batches and all batches met all pre-defined acceptance criteria.

The data from stability studies support the proposed shelf life of 12 months when stored at ≤-60°C.

2.1.2 Drug Product

Process validation had been submitted for 3 consecutive batches and all met pre-defined criteria.

The proposed shelf life is 24 months at ≤-60°C. The product is stored at ≤-60°C during transportation and once the product is received, it will be stored at 2°C to 8°C for 14 days. After drawing into the syringe, the product is to be used within 8 hours. The stability data submitted support the proposed storage condition.

The product is a clear to slightly opaque, colourless to faint white solution, supplied in 10mL crystal zenith vials with two different fill volume, either as 5.5 mL or 8.3 mL.

The analytical protocol and analytical validation data for the product has been evaluated and found to be satisfactory based on the documentation submitted.

The GMP compliance for the drug substance and drug product manufacturer was issued by Health Products Regulatory Authority, Ireland.

2.2 Non-Clinical

- A total of seven pharmacology studies were conducted, involving wild-type mice, SMNΔ7 mice, juvenile Cynomolgus monkeys, and piglets. These studies encompassed various routes of administration, including intravenous (IV), intracerebroventricular (ICV), and intrathecal (IT), utilizing Zolgensma and scAAV9.CBA.GFP vector [similar AAV vector but expressing Green Fluorescent Protein (GFP) instead of SMN] with doses up to 3.3 x 10^{14} vector genomes per kilogram (vg/kg). scAAV9.CBA.GFP vector was included in the early studies to determine the targeting and duration of expression of intended transgene. The studies demonstrated that gene expression patterns were consistent and both vectors exhibited high levels of Central Nervous System (CNS) transduction following single dose administration.

- Two biodistribution studies conducted in mice demonstrated that highest levels of vector genome were generally found in the heart, liver, lung and skeletal muscle.

- In the pivotal OECD GLP compliant toxicology studies, the main target organs of toxicity were limited to the heart and liver in mice. The primary findings in the atrium of the heart were thrombosis and inflammation at a higher dose of 2.4 x 10^{14} vg/kg and the NOEL for atrial thrombosis was 1.5 x 10^{14} vg/kg. The pathogenesis of these atrial findings and the potential translatability to humans is unclear. Liver findings in mice were comprised of dose-related hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. The pathogenesis of Zolgensma related liver findings has not been specifically studied but is likely related to an innate and/or cellular immune response to the viral capsid and/or transgene product.

Environmental Risk Assessment

Zolgensma is a recombinant adeno-associated viral vector based on a naturally occurring AAV, which has been genetically engineered thus rendering it incompetent of replication. The modification has not changed the host range, or tropism of the vector and there are no environmental effects identified that could be caused by release of Zolgensma.

2.3 Clinical Efficacy

- The pivotal clinical studies for Zolgensma consists of three Phase 3 single arm, single dose of 1.1 x 10^{14} vg/kg studies: CL-303 (STR1VE-US), CL-302 (STR1VE-EU) and CL-304 compared with the natural untreated historical cohort from Pediatric Neuromuscular Clinical Research (PNCR) dataset.

Table 1: Summary of Clinical Studies Conducted

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td>Study CL-303 (STR1VE-US)
Phase 3, multicenter, open-label, single-arm, single-dose

Day JW et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol.</td><td>To evaluate the safety and efficacy of Zolgensma in symptomatic SMA Type 1 patients < 6 months with two SMN2 copies</td><td>Co-primary endpoint
1) independent sitting for 30 s or longer at the 18 month of age
2) survival (absence of death or permanent ventilation) at age 14 months

Results

<table>
<tr><th>Endpoint</th><th>Zolgensma (N=22)</th><th>PNCR (N=23)</th></tr>
<tr><td colspan="3">Independent sitting for 30 s or longer at the 18 month of age</td></tr>
<tr><td>n (%)</td><td>13 (59)</td><td>0 (0)</td></tr>
<tr><td>Difference (97.5% CI)
p-value</td><td colspan="2">59 (36, 100)
< 0.0001</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td>2021;20(4):284-293. doi: 10.1016/S1474-4422(21)00001-6.

N = 22</td><td></td><td>
<table>
<tr><td colspan="3">Survival at age 14 months</td></tr>
<tr><td>n (%)
95% CI</td><td>20 (91)
79, 100</td><td>6 (26)
8, 44</td></tr>
<tr><td>Difference (95% CI)
p-value</td><td colspan="2">65 (39, 84)
< 0.0001</td></tr>
</table>
Conclusion
Compared to observations in the PNCR study, Zolgensma demonstrated statistically significant benefit in the two co-primary endpoints.
</td></tr>
<tr><td>Study CL-302 (STR1VE-EU)
Phase 3, multicentre, single-arm, single-dose, open-label

Mercuri E et al; STR1VE-EU study group. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(10):832-841. doi: 10.1016/S1474-4422(21)00251-9.

N = 32</td><td>To evaluate the safety and efficacy of Zolgensma in symptomatic infants (< 6 months) with SMA Type 1 and two SMN2 copies, using broader eligibility criteria (include patients requiring non-invasive ventilatory support for less than 12 h daily or feeding support) than those used in STR1VE-US.</td><td>Primary endpoint
Independent sitting for at least 10 s, at any visit up to the 18 months of age
Secondary endpoint
Survival (absence of death or permanent ventilation) at age 14 months

Results
<table>
<tr><th>Endpoint</th><th>Zolgensma (N=32)</th><th>PNCR (N=23)</th></tr>
<tr><td colspan="3">Independent sitting for at least 10 s, at any visit up to the 18 months of age</td></tr>
<tr><td>n (%)</td><td>14 (44)</td><td>0 (0)</td></tr>
<tr><td>Difference (97.5% CI)
p-value</td><td colspan="2">44 (26, 100)
< 0.0001</td></tr>
<tr><td colspan="3">Survival at age 14 months</td></tr>
<tr><td>n (%)
95% CI</td><td>31 (97)
91, 100</td><td>6 (26)
8, 44</td></tr>
<tr><td>Difference (95% CI)
p-value</td><td colspan="2">71 (48, 87)
< 0.0001</td></tr>
</table>
Conclusion
Zolgensma demonstrated statistically significant benefit in the primary and secondary endpoints compared with untreated PNCR cohort, including for patients requiring non-invasive ventilatory support for less than 12 h daily or feeding support.</td></tr>
<tr><td>Study CL-304
Phase 3, multicenter, open-label, single-arm, single-dose

Cohort 1 (2 copies of SMN2): 14
Cohort 2 (3 copies of SMN2): 15</td><td>To assess the safety and efficacy of Zolgensma in genetically diagnosed and pre-symptomatic patients (≤ 6 months) with SMA having either 2 or 3 copies of SMN2</td><td><u>Cohort 1 (2 copies of SMN2)</u>
Primary endpoint
Independent sitting for at least 10 s, at any visit up to the 18 months of age

Secondary endpoint
Survival (absence of death or permanent ventilation) at age 14 months</td></tr>
</table>

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td></td><td></td><td>
Results
<table>
<tr><th>Endpoint</th><th>Zolgensma (N=14)</th><th>PNCR (N=23)</th></tr>
<tr><td colspan="3">Independent sitting for at least 10 s, at any visit up to the 18 months of age</td></tr>
<tr><td>n (%)</td><td>14 (100)</td><td>0 (0)</td></tr>
<tr><td>Difference (97.5% CI)
p-value</td><td colspan="2">100 (77, 100)
< 0.0001</td></tr>
<tr><td colspan="3">Survival at age 14 months</td></tr>
<tr><td>n (%)</td><td>14 (100)</td><td>6 (26)</td></tr>
<tr><td>Difference (95% CI)
p-value</td><td colspan="2">74 (45, 92)
< 0.0001</td></tr>
</table>

<u>Cohort 2 (3 copies of SMN2)</u>
Primary endpoint
Ability to stand without support for at least 3 seconds at any visit up to 24 months of age

Results
<table>
<tr><th>Endpoint</th><th>Zolgensma (N=15)</th><th>PNCR (N=81)</th></tr>
<tr><td colspan="3">Ability to stand without support for at least 3 seconds at any visit up to 24 months of age</td></tr>
<tr><td>n (%)</td><td>15 (100)</td><td>19 (24)</td></tr>
<tr><td>Difference (95% CI)
p-value</td><td colspan="2">77 (51, 92)
< 0.0001</td></tr>
</table>

Conclusion
Zolgensma provided significant therapeutic benefits to presymptomatic patients with 2 or 3 copies of the SMN2 gene.
</td></tr>
</table>

- Even though the clinical studies were only conducted in infants ≤ 6 months of age who have not received any treatment for SMA, with increasing evidence in the real-world experience with Zolgensma, benefits have been observed in a wider population of patients.

- The current effectiveness data from the RESTORE Registry suggest that patients treated in the RESTORE Registry with either Zolgensma only or patients who switched from nusinersen to Zolgensma are either maintaining or improving their motor function, regardless of age group (0-6 months, ≥ 6 and < 12 months and ≥ 12 and < 24 months).

2.4 Clinical Safety

- The most frequently reported treatment emergent adverse events (TEAEs) were pyrexia, upper respiratory tract infection, constipation, vomiting, and cough.

- The most frequently reported serious adverse events (SAEs) (pneumonia [14.1%]; respiratory distress [7.1%]; and upper respiratory tract infection [6.1%]) are common to children with SMA due to the underlying disease process, and none was considered by the investigator to be related to Zolgensma treatment.

- Adverse events of special interest (AESIs) such as hepatotoxicity, thrombocytopenia, thrombotic microangiopathy, cardiac events and risk of tumourigenicity as a result of vector integration were included as warnings and precautions in the package insert and is part of the Risk Management Plan (RMP).

- No new safety signals have been observed after a cumulative follow-up of up to 8.5 years in Study LT-001 and 4.3 years in Study LT-002 .

- Safety data presented in RESTORE patient registry are consistent with the existing safety profile for Zolgensma. The TEAEs were mainly the AESIs and the events related to the underlying SMA. No neoplasm events were reported.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 393th meeting on 8th February 2024 has decided to approve the registration of this product with the following indication:

Zolgensma is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age:
- with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.