Technology Guidance

Onasemnogene abeparvovec

for treating spinal muscular atrophy

Technology Guidance issued by the Agency for Care Effectiveness based on assessments made by the MOH Drug Advisory Committee and recommendations of the Health Technology Advisory Council

Guidance Recommendations

Onasemnogene abeparvovec is not recommended for inclusion on the MOH Cell, Tissue and Gene Therapy Product List for the treatment of spinal muscular atrophy (SMA) in children under 2 years of age who have Type 1 SMA or up to three copies of the survival motor neuron 2 gene.

This is because the current available evidence is insufficient to show that onasemnogene abeparvovec provides superior long-term efficacy compared to risdiplam, the subsidised disease-modifying treatment for SMA.

Given the current uncertainty in its superiority to risdiplam and its higher treatment cost, it is deemed that the cost-effectiveness of onasemnogene abeparvovec is unfavourable when compared to risdiplam at this time.

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Technology Evaluation

1.1. At the July 2024 and March 2025 meetings, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of onasemnogene abeparvovec for treating spinal muscular atrophy (SMA) in children under 2 years of age who have Type 1 SMA or up to three copies of the survival motor neuron 2 (*SMN2*) gene. This topic was later discussed in May 2025 by the Health Technology Advisory Council ("the Council"), an independent professional body that supports the MOH in determining if financial support for high-cost, high-impact health technologies is appropriate.

1.2. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Clinical and economic evidence for onasemnogene abeparvovec was considered in line with its registered indication.

1.3. The evidence was used to inform the deliberations based on four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the funding considerations.

Assessments made by the MOH Drug Advisory Committee

Clinical need

2.1. In Singapore, about three babies are born with SMA each year. SMA is a neuromuscular disorder that causes muscle weakness and wasting, leading to symptoms such as breathing difficulties and loss of motor function. It is caused by mutations or deletions in the *SMN1* gene and results in a deficiency of the SMN protein. This protein is needed for normal neuron function. The *SMN2* gene also produces a small amount of SMN protein. Patients with fewer copies of the *SMN2* gene and symptom onset at a younger age typically have more severe SMA disease.

2.2. Type 1 SMA is a severe form of the condition, with symptoms appearing within the first 6 months of life. Based on natural history, most individuals with Type 1 SMA cannot control their head movement or sit unassisted. They may also have breathing and swallowing difficulties. Many do not survive beyond 2 years of age due to respiratory failure.

2.3. In Type 2 SMA, symptoms appear between 6 and 18 months of age. Affected individuals can sit without support but cannot stand or walk unaided. They may also have respiratory muscle weakness that can be life-threatening. The lifespan of these individuals varies, but many live into their 20s or 30s.

2.4. Individuals with a genetic diagnosis of SMA but not yet displaying signs or symptoms are considered to have pre-symptomatic SMA. According to clinical experts, treatment during the pre-symptomatic phase may lead to better clinical outcomes, compared with treatment initiation in the symptomatic phase where the disease is more advanced.

2.5. For children with symptomatic or pre-symptomatic SMA, there are three disease-modifying therapies approved by the Health Sciences Authority (HSA). They comprise two drugs (nusinersen and risdiplam) intended for long-term use, and a gene therapy (onasemnogene abeparvovec) administered through a one-time intravenous infusion.

2.6. The Committee acknowledged that risdiplam is currently listed on the Medication Assistance Fund as a subsidised treatment for SMA. They also noted that onasemnogene abeparvovec has a different mechanism of action and represents an alternative treatment option for children with SMA.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence for onasemnogene abeparvovec in children with symptomatic or pre-symptomatic SMA. This included evidence from six single-arm clinical trials, observational studies and overseas registry data.

3.2. Four clinical trials (START, STR1VE-US, STR1VE-EU, and STR1VE-AP) enrolled children with untreated Type 1 SMA and two copies of the *SMN2* gene. Almost all the patients were aged under 6 months in the STR1VE trials and under 8 months in the START trial when they received treatment with onasemnogene abeparvovec.

3.3. From the results of 68 patients across these trials, 91 to 100% of them were alive without the use of permanent assisted ventilation at 14 or 20 months of age. These results were in contrast with the natural history of Type 1 SMA, where only 8 to 26% of untreated children would be expected to survive without permanent ventilation at these timepoints. The trial results also showed that more patients treated with onasemnogene abeparvovec had improvement in motor function and achieved new motor milestones compared with the natural history cohorts.

3.4. The fifth trial (SPR1NT) enrolled 29 children with untreated pre-symptomatic SMA and two or three copies of the *SMN2* gene. These patients were at risk of developing Type 1 or 2 SMA based on their *SMN2* copy numbers. At the time of treatment with onasemnogene abeparvovec, patients were aged 6 weeks or younger.

3.5. Results of the SPR1NT trial showed that all 29 patients were alive without requiring permanent ventilation at 18 or 24 months of age. This was in contrast with the natural history of untreated SMA. More patients treated with onasemnogene abeparvovec had improvement in motor function and achieved new motor milestones compared with the natural history cohorts.

3.6. The sixth trial (SMART) evaluated the use of onasemnogene abeparvovec in 24 patients with heavier body weight (8.5 to 21 kg). Most had Type 2 SMA and three copies of the *SMN2* gene. Notably, 21 patients (88%) had received prior treatment with nusinersen or risdiplam. At baseline, all patients could demonstrate the motor milestones of head control and sitting with support, most (n = 21) could sit without support, and six had achieved the highest possible milestone of standing and walking alone.

3.7. Patients in the SMART trial were aged between 1.5 and 9.1 years when they received treatment with onasemnogene abeparvovec. At 12 months follow-up, most had maintained or improved their baseline motor function.

3.8. Across the six clinical trials, the longest available follow-up data were from 10 patients from the START trial who subsequently enrolled in a long-term follow-up study (LT-001). At the May 2022 data cutoff, all 10 patients were alive without requiring permanent ventilation after a mean duration of 6.9 (range 6.4 to 7.5) years since they had received onasemnogene abeparvovec. All patients maintained their motor milestones previously achieved during the START trial. Three patients also achieved a new milestone – two patients achieved it without any additional drug treatment, while the third patient achieved it after the addition of nusinersen. A total of six patients had received nusinersen and/or risdiplam in the follow-up period.

3.9. In the clinical trials, the adverse reactions most frequently reported with onasemnogene abeparvovec were increased liver enzymes, vomiting and thrombocytopenia. From post-marketing experience, acute serious liver injury and acute liver failure, including fatal cases, have been reported. Therefore, patients who receive onasemnogene abeparvovec would require clinical observation, monitoring of laboratory parameters, and treatment with systemic corticosteroids to mitigate the risk of adverse events.

3.10. Based on available evidence from clinical trials, observational studies and registry data, the Committee noted that onasemnogene abeparvovec provided meaningful treatment benefit in children with SMA. However, the magnitude of benefit was uncertain due to the lack of a comparator arm in the studies.

3.11. The Committee also noted that there was limited data on the long-term efficacy and safety of onasemnogene abeparvovec. Moreover, some patients in the long-term follow-up study received subsequent treatment with nusinersen and/or risdiplam to maximise benefit, so the clinical outcomes observed in those patients might not have been solely attributable to onasemnogene abeparvovec.

3.12. Overall, the Committee considered that the long-term durability of onasemnogene abeparvovec's treatment effect as a one-time gene therapy remained uncertain, especially when compared against drugs such as risdiplam that continually provide an effect through long-term administration.

3.13. The Committee noted that no head-to-head trial between onasemnogene abeparvovec and risdiplam had been conducted. Despite insufficient evidence to ascertain the comparative effectiveness and safety of these treatments, the Committee deemed it reasonable to consider onasemnogene abeparvovec non-inferior to risdiplam in clinical effectiveness and safety for treating SMA in children. They also noted the assessment made by Australia's Pharmaceutical Benefits Advisory Committee (PBAC) that onasemnogene abeparvovec was not expected to provide a substantial and clinically relevant improvement in efficacy or reduction in toxicity over risdiplam for treating SMA.

Cost effectiveness

4.1. Based on the clinical conclusion, the Committee indicated that the cost-effectiveness of onasemnogene abeparvovec could be deemed acceptable if it were cost-minimised to risdiplam. The Committee reviewed a cost-minimisation analysis (CMA) that applied the equi-effective doses of onasemnogene abeparvovec and risdiplam accepted by the PBAC, and a time horizon informed by available evidence of ongoing treatment benefit with onasemnogene abeparvovec. The CMA results showed that, at the price proposed by the company, onasemnogene abeparvovec had a higher treatment cost than risdiplam.

4.2. In addition, the Committee noted that the price-volume agreement (PVA) proposed by the company for onasemnogene abeparvovec was inadequate to manage the uncertainty of the overall budget impact. Overall, the Committee considered that onasemnogene abeparvovec was unlikely to represent an acceptable use of healthcare resources for treating SMA based on the company's pricing proposal.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system was estimated to be between SG$5 million and SG$10 million per year in the first five years of including onasemnogene abeparvovec on the MOH Cell, Tissue and Gene Therapy Product (CTGTP) List for the treatment of SMA, benefitting three patients each year.

Summary

6.1. In view of the unfavourable cost-effectiveness of onasemnogene abeparvovec compared with risdiplam, and the unacceptable PVA proposed by the company, the Committee assessed that onasemnogene abeparvovec was not appropriate for inclusion on the MOH CTGTP List for treating SMA.

Recommendations of the Health Technology Advisory Council

7.1. At the May 2025 meeting, the Council reviewed the evidence presented in ACE's evaluation of onasemnogene abeparvovec and considered the assessments made by the MOH Drug Advisory Committee.

7.2. The Council acknowledged that SMA is a debilitating condition that significantly impacts the health and quality of life of patients. SMA also causes emotional and financial strain on the parents and caregivers of patients.

7.3. The Council considered that onasemnogene abeparvovec offered meaningful treatment benefit for children with SMA compared to the natural history of the disease. However, they had concerns that the long-term efficacy of onasemnogene abeparvovec was uncertain, and that some patients in the follow-up study had received subsequent treatment with nusinersen and/or risdiplam to maintain or optimise clinical benefit.

7.4. The Council acknowledged that risdiplam was currently subsidised for treating children with SMA. They noted there was insufficient clinical evidence to assess whether onasemnogene abeparvovec or risdiplam was a more effective treatment option. However, at the price proposed by the company following multiple rounds of pricing re-submissions, onasemnogene abeparvovec remained at a higher treatment cost than risdiplam, based on a CMA.

7.5. The Council noted that the CMA had applied various assumptions including different time horizons that showed the cost of onasemnogene abeparvovec remained higher than risdiplam. In addition, the analysis did not consider additional costs of subsequent drug treatments that patients might receive after gene therapy.

7.6. Overall, the Council concluded that the current available evidence was insufficient to show that onasemnogene abeparvovec provided superior long-term efficacy compared to risdiplam. Given this uncertainty, the higher cost of onasemnogene abeparvovec treatment could not be justified.

7.7. Therefore, the Council recommended not including onasemnogene abeparvovec on the MOH CTGTP List for the treatment of SMA in children under 2 years of age who have Type 1 SMA or up to three copies of the *SMN2* gene.