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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA — NOVARTIS PHARMACEUTICALS CANADA INC.)
Indication: Spinal muscular atrophy

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that onasemnogene abeparvovec be reimbursed for the treatment of pediatric patients with 5q spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 gene, only if the following conditions are met.

Conditions for Reimbursement
Initiation criteria
1. Genetic documentation of 5q spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 gene.
2. Patients who are:
   2.1. symptomatic or pre-symptomatic with one to three copies of the survival motor neuron 2 gene
   2.2. 180 days of age or younger
   2.3. not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive).

Prescribing conditions
1. Patient must be under the care of a specialist with experience in the diagnosis and management of spinal muscular atrophy.
2. Reimbursement is limited to one lifetime administration of onasemnogene abeparvovec.

Pricing conditions
1. A reduction in price.

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ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA — NOVARTIS PHARMACEUTICALS CANADA INC.)

Indication: Spinal muscular atrophy.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that onasemnogene abeparvovec be reimbursed for the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene, only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria

1. Genetic documentation of 5q SMA with biallelic mutations in the SMN1 gene.
2. Patients who are:
   - 2.1. symptomatic or pre-symptomatic with one to three copies of the SMN2 gene
   - 2.2. 180 days of age or younger
   - 2.3. not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive).

Prescribing conditions

1. Patient must be under the care of a specialist with experience in the diagnosis and management of SMA.
2. Reimbursement is limited to one lifetime administration of onasemnogene abeparvovec.

Pricing conditions

1. A reduction in price.

Reasons for the Recommendation

1. One phase III, single-arm study, STR1VE-US (N = 22), enrolled patients diagnosed with SMA who were symptomatic or pre-symptomatic with one or two copies of the SMN2 gene. Patients were younger than 180 days of age at the time of infusion of onasemnogene abeparvovec, had normal swallowing function, and minimal need for non-invasive ventilation. Patients were excluded if they required any form of invasive ventilatory support. STR1VE-US demonstrated that 59% (97.5% confidence interval [CI], 34% to 81%) of patients were able to sit independently for at least 30 seconds at 18 months of age, and 90% (97.5% CI, not reported) were alive without permanent ventilation at 14 months of age. The magnitude of the observed benefits is clinically meaningful compared with outcomes from a historical cohort of patients with one or two copies of the SMN2 gene (selected from the Pediatric Neuromuscular Clinical Research Network [PNCR] dataset) who received standard of care treatment and from the known natural history of SMA in patients with one or two copies of the SMN2 gene.
2. One phase III, ongoing, single arm study, SPR1NT (N = 30), enrolled pre-symptomatic infants younger than six weeks who had either two copies of the SMN2 gene (N = 14) or three copies of the SMN2 gene (N =15). Interim analysis results showed that all infants were alive without permanent ventilation (event-free survival) at 14 months, and 57% of infants with two copies and 67% of those with three copies of the SMN2 gene achieved independent sitting for at least 30 seconds at any time up to 18 months of age. As well, 27% and 13% of infants with three copies of the SMN2 gene managed to stand without support for at least 3 seconds or to walk alone at any time up to 24 months of age, respectively. Overall, results from SPR1NT suggested benefit from treatment of pre-symptomatic patients who have two or three copies of the SMN2 gene with onasemnogene abeparvovec.
3. CADTH reanalysis of a cost-utility model submitted by the sponsor found that onasemnogene abeparvovec was unlikely to be cost-effective at the submitted price, with an estimated incremental cost-effectiveness ratio (ICER) of $334,090 per quality-adjusted life-year (QALY) compared with best supportive care (BSC). The estimated cost-effectiveness is associated with significant uncertainty because the comparative effectiveness of onasemnogene abeparvovec and nusinersen could not be determined and most of the modelled benefits with onasemnogene abeparvovec were accrued in time periods beyond which any clinical data are available. A price reduction of at least 90% is required for onasemnogene abeparvovec to achieve an ICER below $50,000 per QALY gained.

Implementation Considerations

- Genetic testing required to confirm the presence of biallelic mutations in the SMN1 gene is not currently available in all jurisdictions. Given the need for early initiation of treatment for SMA, the uncertainty regarding the availability of these screening tests and the potential for such tests to place an additional financial burden on the public health care system, CDEC suggested that the sponsor should be required to ensure that these tests are available and financed to support the implementation of the reimbursement of onasemnogene abeparvovec.
- SMA is associated with irreversible loss of motor neurons and motor nerves; therefore, clinical experts recommend the earliest possible initiation of therapy. Jurisdictions that do not currently have newborn screening programs may wish to consider implementing such programs to maximize the potential health gained from administration of onasemnogene abeparvovec.
- Permanent ventilation was defined in the included studies as the need for a tracheostomy or requirement of 16 hours or more of respiratory assistance per day (via non-invasive ventilatory support) for 14 or more consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.
- The economic analysis was associated with substantial uncertainty regarding the cost-effectiveness of onasemnogene abeparvovec, due largely to the uncertainty associated with the long-term efficacy of the treatment. Extrapolation of clinical benefit was based on assumptions, and the associated structural uncertainties could not be adequately tested due to limitations within the submitted model. Treatment with onasemnogene abeparvovec is anticipated to be less cost-effective in patients with less severe disease (this group will include many patents with three copies of the SMN2 gene), which would justify a higher price reduction; however, the available evidence was insufficient to estimate the size of this reduction. Given the extent of uncertainty regarding the cost-effectiveness of this product and the extremely high cost of treatment, jurisdictions may wish to consider establishing product listing agreements that mitigate the long-term financial risk to public payers.
- Sequencing of onasemnogene abeparvovec relative to other medications indicated for the treatment of SMA is an important evidence gap. CDEC noted that children who have been receiving medications indicated for SMA — such as nusinersen, which has a difficult mode of administration and potential for related adverse events — and who meet the initiation conditions above should not be precluded from having treatment with onasemnogene abeparvovec reimbursed. Clinical experts for CADTH suggested that once onasemnogene abeparvovec is administered, no further treatment with nusinersen or other medications indicated for treatment of SMA should be expected. There are currently no data on the effectiveness of nusinersen or other medications indicated for SMA administered after onasemnogene abeparvovec.

Discussion Points

- SMA is a rare, genetic, life-threatening, and seriously debilitating neuromuscular disorder that has a heavy burden on patients, caregivers, society, and the health care system. Nusinersen is currently the only other approved drug treatment for patients with SMA. Despite the availability of nusinersen, CDEC heard patient and clinical expert input that there remains a need for additional safe and effective treatments for SMA. CDEC noted patient and clinician concerns regarding the potential for harm when administering nusinersen intrathecally every three months and uncertainty that the intended dose consistently reaches the site of action, which could lead to progressive bulbar muscle weakness in some patients.
- Improving and/or maintaining respiratory and bulbar function in patients with SMA are important goals identified by patient and clinician input. These were assessed as secondary outcomes in the STR1VE-US study. The percentage of patients with the ability to thrive (as assessed by the ability to tolerate thin liquids, no requirement for mechanical support for nutrition, and maintenance of weight above the third percentile for age and sex) at 18 months was 41% (97.5% CI, 19% to 66%). The percentage of patients who were independent of ventilatory support was 82% (97.5% CI 45% to 86%) at 18 months.
- CDEC identified numerous limitations associated with the single-arm trial design of the STR1VE-US and the SPR1NT studies. Although CDEC considered the observed treatment effects of onasemnogene abeparvovec on assessed outcomes in both studies to be clinically meaningful, the lack of a concurrent control group precludes a precise estimation of the magnitude of benefit.
- The use of a natural history cohort in the STR1VE-US and the SPR1NT studies did not allow for unbiased estimates of treatment effect given important differences in patient characteristics, collateral treatments, time frames over which patients were observed, and the lack of statistical adjustment for such differences.
- Additional key limitations of the STR1VE-US study were the use of unblinded assessors and the limited time horizon of 18 months for a life-long condition. The SPR1NT study was similarly limited by 18-month (infants with 2 copies of the SMN2 gene)

and 24-month (infants with 3 copies of the SMN2 gene) time horizons, and because results were from interim analyses. The duration of the treatment effect with onasemnogene abeparvovec is unclear.

- The generalizability of the results from the STR1VE-US and the SPR1NT studies to other patients with SMA (including different functional capabilities, ages, and SMN2 copy numbers), and patients who were previously treated with medications for SMA, such as nusinersen, was also noted as an important limitation.
- The reviewed evidence came from studies of children younger than six months at the start of treatment. Patients enrolled in the STR1VE-US study had to be symptomatic and younger than six months (180 days) at the time of onasemnogene abeparvovec infusion (mean age at baseline was 3.7, standard deviation [SD] 1.6, range 0.5 to 5.9 months). Eligibility criteria in a phase I, open-label, single-infusion, ascending-dose, single-center study (START; N = 12 in the therapeutic dose cohort) required patients be symptomatic and six months and younger with disease onset up to six months of age (mean age at baseline was 3.1, SD 2.06, range 0.9 to 7.9 months). Patients enrolled in SPR1NT were pre-symptomatic and younger than 6 weeks. The other ongoing studies have also restricted eligibility to those younger than six months. Therefore, the effectiveness of treatment with onasemnogene abeparvovec in patients older than six months is unknown based on the currently available evidence.
- Nusinersen was identified as the key comparator for onasemnogene abeparvovec as it is the only other medication currently approved and reimbursed for the treatment of SMA. However, there are no studies directly comparing the two treatments for SMA. Two sponsor-funded indirect treatment comparisons (ITCs) between onasemnogene abeparvovec and nusinersen were not useful for making inferences about the comparative efficacy and safety of nusinersen and onasemnogene abeparvovec because of significant limitations with the comparability of the included studies and uncertainty regarding whether the basic assumptions of the analyses were met.
- CDEC discussed results from additional studies provided by the sponsor. The results from the studies generally supported the efficacy of treatment with onasemnogene abeparvovec. The additional studies were single-arm, interventional studies without comparison to other treatments or external cohorts. As well, several of these studies are ongoing and few results are available, including for the STR1VE-EU study (N = 30), which had a similar design and entry criteria as the STR1VE-US study.
- The economic evidence submitted to CADTH was derived from the STR1VE-US study, and only patients with two copies of the SMN2 gene. The sponsor submitted a scenario analysis that considered patients with three SMN2 copies, based on interim data from the SPR1NT study. No information was submitted that included patients with one SMN2 copy. Given the limited information on the clinical and cost effectiveness of onasemnogene abeparvovec in patients with 1 or 3 copies of SMN2, it is not possible to estimate the price reductions that will be needed to improve the cost-effectiveness.
- CDEC noted that regulatory agencies have identified safety concerns related to liver injury, increased troponin levels, and thrombocytopenia. CDEC also noted the issue of the emergence of antibodies to the adeno-associated virus (AAV) capsid vector that delivers onasemnogene abeparvovec would likely preclude any benefit from a second injection. The product monograph for onasemnogene abeparvovec states that an immune response to the AAV capsid will occur after infusion of onasemnogene abeparvovec; therefore, patients should not receive a second dose of onasemnogene abeparvovec. Given these safety concerns and the limited duration of the study treatment periods, the long-term balance of safety and efficacy for onasemnogene abeparvovec is unknown.

Background

Onasemnogene abeparvovec has a Health Canada indication for the treatment of pediatric patients with 5q SMA with biallelic mutations in the SMN1 gene and three or fewer copies of SMN2 gene, or infantile-onset SMA. The product monograph states that the efficacy and safety of onasemnogene abeparvovec in pediatric patients eight months of age and older at the time of infusion have not been established in clinical trials.

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that uses AAV9 capsid to deliver a stable, fully functional human SMN transgene. It acts to promote the survival and function of transduced motor neurons by providing an alternative source of SMN protein expression in motor neuron.

Onasemnogene abeparvovec is available as a solution for IV infusion. Kits contain between two and 14 vials with 2×10^{13} vector genomes (vg) per mL. Onasemnogene abeparvovec is administered as a one-time IV infusion with a recommended dose of 1.1×10^{14} vg/kg. In addition, prednisolone treatment should be administered at 1 mg/kg per day (or equivalent) one day before onasemnogene abeparvovec infusion and continued for 30 days, then tapered over the next 28 days (or as appropriate based on the corticosteroid being administered) in patients with unremarkable findings related to liver function (normal clinical exam, total bilirubin,

and alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels below two times the upper limit of normal). The product monograph also recommends monitoring the following:

- Platelet count weekly for the first month and every other week for the second and third months. Continue monitoring until platelet count results are unremarkable.
- Troponin-I levels before onasemnogene abeparvovec infusion and monitor for at least three months after until levels are unremarkable. If elevations in troponin-I levels persist or worsen, consider additional cardiac function monitoring and follow-up, including consultation with a pediatric cardiologist.
- Anti-AAV9 antibodies before onasemnogene abeparvovec infusion. Patients with titers higher than 1:50 should not be treated with onasemnogene abeparvovec.

Submission History

This is the first indication for which onasemnogene abeparvovec has been reviewed by CADTH and CDEC.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of clinical trials on onasemnogene abeparvovec, a summary and critique of two sponsor-provided indirect comparisons, a summary and critique of other relevant evidence, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with SMA and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups provided input, Cure SMA Canada (CSMAC) and Muscular Dystrophy Canada (MDC). The submissions were based on semi-structured interviews and surveys. Together, the two patient groups collected responses from 572 patients and family members.

Patient input from CSMAC highlighted that SMA "impacts every aspect of a patient's life, from physical health, family dynamics, mental health, and longevity". Similarly, the patient input received from the MDC highlighted four key themes; negative impact on mental and emotional well-being, loss of patient independence, increased load on families, and difficulty breathing, swallowing and loss of mobility. As SMA progresses, patients lose the ability to walk, perform daily hygiene tasks or even swallow and breathe independently. In addition, "most patients are unable to perform their own personal care activities." The most concerning aspects of SMA are difficulties breathing and swallowing. Parents indicated that "their children showed the inability to breathe properly from very early in life, they lost their ability to swallow, requiring regular suctioning, positioning and hospitalizations." The burden of this disease can be extraordinarily high for caregivers.

Currently, nusinersen is available as a treatment for SMA. Respondents indicated a wide range of experience with nusinersen, from no clear benefits to "definitely beneficial" with one parent reporting "improved quality of life" shortly after treatment initiation. Patients and parents expressed concern and anxiety about the quarterly intrathecal administration of nusinersen, a painful and invasive procedure required for the patient's lifetime, which is particularly challenging for young children.

Patients and their families expressed enthusiasm and high expectations for onasemnogene abeparvovec treatment considering the one-time infusion and the mechanism of action. Families affected by SMA are very hopeful that onasemnogene abeparvovec will improve the overall quality of life of people with SMA by improving motor function, respiratory function, and feeding, and by stopping disease progression. Some respondents believe the gene therapy "could be a cure" and "if children are treated pre-symptomatically, they could potentially live normal lives".

Clinical Trials

The systematic review included one study, STR1VE-US (N = 22). the STR1VE-US study (also known as CL-303) was a phase III, open-label, single-arm, single-dose study that investigated the efficacy and safety of onasemnogene abeparvovec in infants with SMA type 1 who were symptomatic or pre-symptomatic with one or two copies of SMN2 (inclusive of the known SMN2 gene modifier mutations [c.859G>C]). The study was conducted in multiple centres in the US and enrolled a total of 22 SMA patients. Patients enrolled in the STR1VE-US study were given one-time intravenous infusion of onasemnogene abeparvovec at 1.1×10^{14} vg/kg. In addition, patients received prophylactic prednisolone at approximately 1 mg/kg per day beginning 24 hours before gene replacement therapy until at least 30 days post-infusion in accordance with the protocol-specified guidelines for steroid tapering.

A total of 22 patients were enrolled in the STR1VE-US study and were given onasemnogene abeparvovec. Overall, 54.4% were females, 50.0% were white, the onset of symptoms was reported at a mean age of 1.9 months ([SD = 1.2), all patients had two copies of SMN2, and none required feeding support or ventilatory support at baseline. At study baseline, enrolled patients had a mean age of 3.7 months (SD = 1.6) and a mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score of 32.0 (SD = 9.7).

The key limitation of the STR1VE-US study was the absence of a concurrent control arm in the form of a placebo control or an active control, leading to a potential overestimate of treatment effect for onasemnogene abeparvovec in the single arm trial. Without a randomized comparison to a control group, natural fluctuations in the disease cannot be adjusted for, nor can the effects of known and unknown confounders. Comparison to similar outcome measures in the PNCR dataset, while useful to reflect the natural history of the disease, is limited by differences in patient characteristics between the two populations (patients in the PNCR dataset were older at symptoms onset, had a lower CHOP INTEND score, and required more feeding support and more ventilatory support) that could impact response to treatment or outcome regardless of treatment. The PNCR dataset and STR1VE study populations are different based on a period-cohort basis; PNCR enrolled patients between May 2005 and April 2009, several years before the start date of the STR1VE-US study (October 24, 2017). As well, no statistical analytical methods were used to account for differences between patients in the STR1VE-US study and the PNCR dataset.

Investigators and outcome assessors in the STR1VE-US study were aware that patients have received onasemnogene abeparvovec infusion. The STR1VE-US study did not include patients six months of age or older, who required nutritional or ventilatory support, or who had more than two copies of SMN2.

Outcomes

Outcomes were defined a priori in the CADTH systematic review protocol. Of these, the committee discussed the following:

- motor function related outcomes
- respiratory related outcomes
- survival
- health-related quality of life
- safety outcomes.

The STR1VE-US study measured two co-primary outcomes: functional independent sitting at 18 months of age (defined as ability to sit alone ≥30 seconds) and survival at 14 months of age (defined as avoidance of death or permanent ventilation). Additionally, the STR1VE-US study measured two co-secondary outcomes — maintenance of ability to thrive and independence of ventilatory support — along with several exploratory outcomes. The results of the co-primary outcomes for the STR1VE-US study were contrasted with the results of a natural history cohort from the PNCR dataset. The PNCR dataset gathers retrospective and prospective data for patients with SMA who are managed in Harvard University/Boston Children's Hospital, Columbia University, and the University of Pennsylvania/Children's Hospital of Philadelphia. The PNCR natural history cohort was comprised of 23 patients with SMA type 1 (symptoms onset before six months of age and 2 copies of SMN2).

Efficacy

By 18 months of age, 59.1% of patients (13 out of 22; 97.5% CI, 33.6% to 81.4%; P <0.0001) enrolled in the STR1VE-US study achieved the co-primary outcome of independent sitting for at least 30 seconds, compared to a historical control rate of 0% (0 out of 23) patients in the PNCR natural history cohort.

The co-primary outcome of the proportion of patients with event-free survival (no death or permanent ventilation) showed that 90% of patients (20 out of 22; 97.5% CI, not reported; P <0.0001) were able to survive until 13.6 months of age without the need for permanent ventilation. In contrast, 26.1% of patients (6 out of 22; 97.5% CI, not reported) in the PNCR dataset natural history cohort reached the age of 13.6 months without the need for permanent ventilation.

For the co-secondary outcome, maintenance of ability to thrive at 18 months, 40.9% of patients (9 out of 22; 97.5% CI, 18.6% to 66.4%; P < 0.0001) achieved all three criteria for this outcome (able to tolerate thin liquids, does not receive nutrition through mechanical support, and maintains weight consistent with age). Onasemnogene abeparvovec also demonstrated benefit for the other co-secondary outcome, independence from daily ventilatory support (in the absence of acute reversible illness and excluding perioperative ventilation) at 18 months; 81.8% of patients (18 out of 22; 97.5% CI, 45.1% to 86.1%; P < 0.0001) achieved this outcome.

Assessment of various motor milestones indicated that most patients (85.0%, 17 out of 20) were able to hold their head erect unsupported and over half were able to roll (59.0%, 13 out of 22) and sit alone for 10 seconds or longer (63.6%, 14 out of 22). One patient was able to achieve the motor milestones of crawling, pulling to stand, stand with assistance, stand alone, and walk with assistance.

Harms (Safety)

At least one adverse event was reported in all enrolled patients. Pyrexia was reported by the largest percentage of patients (54.5%), followed by upper respiratory tract infection (50%), constipation (40.9%), and scoliosis (40.9%), although the latter was likely a signal of disease progression instead of a drug-related adverse event. Serious adverse events were reported in 45% of patients, with most of the serious adverse events related to respiratory problems or respiratory infections. Two patients withdrew from treatment due to adverse events (one died and the other withdrew after experiencing respiratory distress). The cause of death for the one patient who died was determined by the study investigators to be unrelated to onasemnogene abeparvovec.

An increase in the aminotransferase levels occurred in approximately one-quarter of patients treated with onasemnogene abeparvovec in the STR1VE-US study (27% had elevated AST and 23% had elevated ALT).

[redacted]

Thrombocytopenia was recorded in 9.1% of patients.

Indirect Treatment Comparisons

Two ITCs were reviewed: a sponsor-provided ITC and a published ITC by Dabbous et al. that was funded by the sponsor. Both ITCs aimed to assess the comparative efficacy of onasemnogene abeparvovec versus nusinersen in patients with SMA type 1. Dabbous et al. used data from the nusinersen ENDEAR study and from the onasemnogene abeparvovec START study (see Other Relevant Evidence) to conduct unanchored naive Bayesian and frequentist comparisons. The sponsor-provided ITC used data from the ENDEAR study (plus its long-term extension study, SHINE) and the START and STR1VE-US studies to perform an unanchored, naive Bayesian comparison and an unanchored matched adjusted indirect comparison (MAIC).

Both unanchored naive Bayesian analyses suggested that onasemnogene abeparvovec was favoured over nusinersen in both base-case and sensitivity analyses for the survival and motor milestone achievement outcomes, and for avoidance of permanent assisted ventilation in the Dabbous et al. analysis. Using the unanchored MAIC approach, in which adjustment could only be made for baseline CHOP INTEND score and baseline nutritional support, onasemnogene abeparvovec was favoured over nusinersen in event-free survival. The unanchored MAIC did not favour either intervention for overall survival.

Only the sponsor-provided ITC assessed adverse events. The reported differences in adverse events between onasemnogene abeparvovec and nusinersen were associated with unrealistically large estimates and very wide credible intervals.

The results from the ITCs are associated with serious limitations related to the differences in study designs, study entry criteria, patient characteristics, and outcome definitions between the nusinersen and onasemnogene abeparvovec trials. Considering the lack of proper anchoring for the indirect comparisons and the inability to control for the considerable heterogeneity in the included studies, the basic assumptions behind the ITCs are unlikely to have been met. As such, the results of these analyses are not considered valid for the purposes of decision making.

Other Relevant Evidence

The SPR1NT study (N = 30), is an ongoing phase III, multicenter, open-label, single-arm, global clinical trial for onasemnogene abeparvovec in infants younger than six weeks at the time of infusion, diagnosed with pre-symptomatic SMA with bi-allelic deletion of the SMN1 gene and two or three copies of the SMN2 gene. The intervention was a one-time intravenous infusion of 1.1×10^{14} vg/kg onasemnogene abeparvovec. The planned follow-up was up to 18 months of age for patients with two copies of the SMN2 gene (Cohort 1; N = 14) and up to 24 months for those with three copies of the SMN2 gene (Cohort 2; N = 15). For the primary efficacy outcome of Cohort 1, 57.1% of infants achieved independent sitting for 30 seconds or longer at any time up to 18 months of age, which was statistically significantly greater than the null value of 0.1% (97.5% CI, 25.8% to 84.7%; P < 0.0001) derived from natural history cohorts sampled from the PNCR and NeuroNEXT datasets. The percentage of infants in Cohort 2 who achieved this outcome was 66.7% (97.5% CI, [redacted]). Greater than one-quarter of infants (26.7%) were able to stand without support for three seconds or longer at any time up to 24 months of age; this was the primary efficacy outcome of Cohort 2 (it was not evaluated for those in Cohort 1) but no statistical comparisons or confidence intervals were reported. All infants in both cohorts survived event-free (defined as avoidance of death or the requirement of permanent ventilation) at 14 months of age. [redacted] in Cohort 1 and [redacted] in Cohort 2 maintained the ability to thrive (i.e., maintained body weight at or above the third percentile without the need for non-oral or mechanical feeding support) at 12 months of age. Two patients (13.3%) in Cohort 2 walked without support milestone at any time up to 24 months of age; this outcome was not evaluated in Cohort 1. Adverse events were similar to those observed in the STR1VE-US study. The lack of a concurrent comparator group and comparisons with the natural history cohorts may overestimate the benefits of onasemnogene abeparvovec treatment in infants who are pre-symptomatic and have two or three copies of the SMN2 gene. However, the outcomes evaluated in the study were objective and clinically relevant, which may mitigate some of the design limitations.

The START study (N = 15) was a phase I, single-center, open-label, single-infusion, ascending-dose clinical trial to evaluate the safety and efficacy of two doses of onasemnogene abeparvovec (Cohort 1 received 6.7×10^{13} vg/kg, n = 3; Cohort 2 received the therapeutic dose 2.0×10^{14} vg/kg, n = 12). Patients were younger than six months with a bi-allelic SMN1 mutation (deletion or point-mutation) and two copies of the SMN2 gene, consistent with SMA type 1. Of note, the original protocol allowed infants up to the age of nine months to be eligible. This inclusion criterion was revised to include patients six months or younger; nine patients were enrolled before this change with an age range of nine months or younger. Patients were observed for two-years following the single infusion. Patients could continue into the 15-year START long-term extension study.

Two ongoing studies, STR1VE-EU and STR1VE-AP, have the same study design, entry criteria, intervention, and outcomes as the STR1VE-US study, except that they are enrolling patients living in Europe and Asia (specifically Japan, Korea, and Taiwan), respectively.

The preliminary nature of the results from the ongoing STR1VE-EU study makes it difficult to draw conclusions beyond the results being supportive of those from STR1VE-US.

Cost and Cost-Effectiveness

All kits supplying onasemnogene abeparvovec are priced at $2,910,500 which is the one-time, total drug acquisition cost.

The sponsor submitted a cost-utility analysis assessing onasemnogene abeparvovec compared to nusinersen, and BSC, for the treatment of patients with SMA type 1 with an onset of symptoms at six months of age or younger, who are symptomatic at baseline, and have two copies of the SMN2 gene. The modelled population differs from the Health Canada indication and funding request,

which do not specify SMA type 1 or restrict to patients with symptoms. The economic analysis was undertaken over a lifetime time horizon (80 years) from the perspective of the public health care payer. The cohort-state transition model (Markov) consisted of five health states based on motor function milestones achieved by the patient, including: *within a broad range of normal development*, *walking unassisted*, *sitting unassisted*, *unable to sit unassisted*, and *requiring permanent assisted ventilation*. The model consisted of two phases. The first phase (early) captured patient movement between health states within the first 30 months of treatment with onasemnogene abeparvovec and 40 months for patients on nusinersen based on the observed clinical trial data for patients on pharmacotherapy. Data from the START and STR1VE-US studies informed a MAIC for the comparison between onasemnogene abeparvovec and nusinersen. A naive comparison was conducted for onasemnogene abeparvovec compared with BSC, with natural history cohort data used to inform the efficacy of BSC. The second phase (extrapolated) was a long-term extrapolation (remaining 77 years of the model time horizon) used to model patient survival according to natural history data based on the patient's health state at the end of the early phase of the model. The sponsor submitted an additional scenario analysis based on interim data from the SPR1NT study to reflect patients with three copies of the SMN2 gene.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The magnitude of clinical benefit, with regards to motor milestone achievement and survival (i.e., mortality and requirement of permanent ventilation), with onasemnogene abeparvovec compared with BSC, and nusinersen, is highly uncertain. A naive comparison approach was used for BSC, which introduced a high level of uncertainty to these results. The ITC technique used by the sponsor was insufficient to establish the comparative effectiveness of nusinersen. There is also no evidence for the long-term comparative efficacy and safety of onasemnogene abeparvovec or nusinersen, adding to the uncertainty.
- The target population in the model (symptomatic patients) does not include all patients who are likely to receive onasemnogene abeparvovec, such as pre-symptomatic patients.
- The submitted model structure may not appropriately capture all key changes in patient health-related quality of life, including SMA-related developments such as the requirement for nutritional support or loss in functional status, for patients other than those who discontinue nusinersen.
- Several issues were identified with assumptions relating to the utility values used, which biased incremental QALYs in favour of onasemnogene abeparvovec.
- Issues were identified with ventilation costs and with an inappropriate assumption that SMA patients could be "within a broad range of normal development", which biased costs and QALYs in favour of onasemnogene abeparvovec.

CADTH conducted a reanalysis to address some of the identified limitations. It assumed equal motor milestone achievement and survival for both patients receiving onasemnogene abeparvovec and nusinersen, removed utility increments for patients in the *unable to sit unassisted* or *sitting unassisted* health states, assigned utility values to the *walking unassisted* and *requiring permanent assisted ventilation* health states to align with the expectations of clinical experts, and updated permanent ventilation costs. Although CADTH reanalyses were in line with those of the sponsor, the key limitations pertaining to the lack of longer term and comparative clinical information could not be addressed and remains a key issue for the interpretation of the results. CADTH estimated that onasemnogene abeparvovec is associated with an ICER of $334,090 per QALY compared with BSC, and onasemnogene abeparvovec dominates nusinersen. Compared with BSC, onasemnogene abeparvovec would not be considered cost-effective at a conventional willingness-to-pay threshold. A price reduction of more than 90% is required for onasemnogene abeparvovec to be considered the cost-effective strategy compared to BSC at a willingness-to-pay threshold of $50,000 per QALY.

Several major limitations could not be addressed, most importantly the lack of information on the long-term comparative clinical effectiveness of onasemnogene abeparvovec versus comparators. Within the model, 96% and 98% of the QALY benefit of onasemnogene abeparvovec compared with BSC and nusinersen, respectively, was estimated beyond the observed trial period. The cost of nusinersen is a key cost driver but the actual price for participating plans is unknown. Additionally, the sponsor's base case analysis only considered patients with SMA type 1 and two copies of the SMN2 gene who were younger than two years of age and symptomatic at baseline before six months of age, rather than the full indicated population. A scenario analysis submitted by the sponsor suggested that the conclusions drawn from the CADTH reanalysis may be broadly applicable to Type 1 SMA patients with three SMN2 copies who were pre-symptomatic at baseline, but limitations within the clinical data make the results from this analysis highly uncertain. No information was submitted for patients with one copy of the SMN2 gene, and the cost-effectiveness in this

population is unknown. Because of these limitations, caution should be exerted in the interpretation of the health economic results. The cost-effectiveness of onasemnogene abeparvovec in patients older than six months of age is unknown.

Request for Clarification

The drug plans that participate in the CADTH reimbursement review process filed a request for clarification during the embargo period for the CDEC recommendation of onasemnogene abeparvovec. The questions posed by the drug plans and responses from CDEC are summarized below.

Based on patient characteristics such as the number of SMN2 copies, SMA type, age of symptom onset, etc., which patient populations are the most likely to benefit from treatment with onasemnogene abeparvovec?

CDEC Response

The patient population of the currently available completed (STR1VE-US and START) and ongoing studies (SPR1NT, STR1VE-EU, and ST1VE-AP) are similar in that infants with 1 to 3 copies of the SMN2 gene, are symptomatic or pre-symptomatic, and have received their onasemnogene abeparvovec infusion within the first six months of life (except for less than 9 infants in START) were enrolled. In addition, patients could not require permanent feeding or ventilatory support to be eligible for the studies. Therefore, the best available data for the effects of onasemnogene abeparvovec are based on patients who have symptomatic Type 1 SMA or who are likely to develop it (pre-symptomatic). Infants with this type never achieve the motor milestone of sitting unsupported and have limited survival beyond two years of age due to respiratory failure. As described in the Reasons for Recommendation, children treated with onasemnogene abeparvovec achieved clinically meaningful outcomes compared what was expected based on natural history data.

Although there remains considerable uncertainty regarding which patients are most likely to benefit, this question cannot be resolved at this time.

The CDEC recommendation specifies the SMA population that should receive reimbursement for treatment with onasemnogene abeparvovec based on the currently available evidence.

Similarly, could CDEC please identify the SMA patient populations for which there is no evidence of benefit from treatment with onasemnogene abeparvovec?

CDEC Response

The Discussion section from the CADTH clinical review report summarizes the gaps in available body of evidence well:

- The comparative efficacy of onasemnogene abeparvovec versus nusinersen
- The efficacy of onasemnogene abeparvovec in patients with SMA who have been previously treated with nusinersen
- The efficacy of onasemnogene abeparvovec in patients who need ventilatory support for longer than 16 hours daily
- The efficacy of onasemnogene abeparvovec in patients who may require feeding support through invasive mechanical methods or who have difficulty swallowing with signs of aspiration
- The efficacy of onasemnogene abeparvovec in pre-symptomatic patients with genetic diagnosis of SMA who have four or more copies of the SMN2 gene
- The efficacy of onasemnogene abeparvovec in patients with SMA who are older than six months of age
- The efficacy of onasemnogene abeparvovec in patients with SMA who are older than six months of age and are on ventilatory support, parenteral feeding, or are wheelchair bound
- The efficacy of onasemnogene abeparvovec in patients with symptomatic SMA with three or more copies of SMN2 and older than six months
- The efficacy of onasemnogene abeparvovec in patients who are diagnosed with, or likely to have, SMA type 2, 3, or 4
- The efficacy of onasemnogene abeparvovec beyond 24 months after infusion.

Is there evidence to suggest that there is a maximum weight above which patients would not be expected to benefit from treatment with onasemnogene abeparvovec? If so, what is this maximum weight? Is there a maximum weight that puts patients at higher risk for adverse events, or are adverse events linked to age?

CDEC Response

CADTH reviewers reported that based on animal models and the results of the dose finding study, START, the dose of onasemnogene abeparvovec was set at 1.1 x 10^{14} vg/kg. To achieve the intended therapeutic dose, the total amount of administered onasemnogene abeparvovec will be determined by patient weight. The patients included in the reviewed had a weight range of 2.6 kg up to 8.5 kg. No subgroup analyses for patients by baseline body weight or any other analysis describing an association between body weight and efficacy outcomes or adverse events were identified.

Input from clinical experts also indicated that a maximum body weight limit would not be considered in practice settings.

CDEC concluded there is no evidence to inform this question.

Is age the most appropriate treatment cut-off, or is there another factor that the participating drug programs should consider (e.g., weight of patients)?

CDEC Response

Type 1 SMA is considered the most common and severe manifestation of SMA. These patients have a small chance of survival beyond two years of age. A distinguishing feature of Type 1 SMA is symptoms onset within their first six months of living, in addition to never achieving motor milestones such as sitting unsupported. These patients typically have one to three copies of the SMN2 gene. Symptom onset between six months to 18 months are a distinguishing feature of Type 2 SMA, where patients commonly survive past the age of 25 years. These patients typically have three or more copies of the SNM2 gene. This clinical classification system of SMA emphasizes that an earlier onset of symptoms is associated with a worse prognosis.

Since SMA causes irreversible loss of motor neuron, the longer the disease duration is, the less benefit a patient would receive from any SMA disease-modifying therapy.

Clinical expert input stated that age, time to symptom onset, and SMN2 gene copy number are the most important factors in clinical practice.

No evidence was identified to inform a cut-off based on body weight within the sponsor's submission.

CDEC concluded that body weight is not appropriate for determining initiation, renewal, or discontinuation conditions for the reimbursement of onasemnogene abeparvovec.

Can CDEC confirm how the available data from the ongoing SPR1NT study were considered and factored into the current recommendation? Acknowledging uncertainty, data described in the CADTH Clinical Review Report appear to suggest that patients with 3 copies of the SMN2 gene could experience substantial reductions in morbidity in a disease where there is significant unmet medical need.

CDEC Response

Overall, the quality of the data in the SPR1NT study is similar to that in the STR1VE-US study; both are small natural history cohort comparator studies with no concurrent comparator groups, although the SPR1NT study results were based on interim not final analyses. Health Canada considered the results of the SPR1NT study robust enough to inform the indication. Therefore, the data from the SPR1NT study were considered for a reimbursement recommendation.

The SPR1NT study included only infants younger than six weeks of age who were pre-symptomatic. Generalizing the results to infants who are symptomatic is reasonable given the natural history of SMA. Similarly, although there is an absence of strong empirical evidence, biology and clinical experience (based on the clinical expert input) argue in favour of generalizability of the results in patients younger than six weeks to those who are younger than six months.

CDEC acknowledged that a challenge is that some infants with three copies of the SMN2 gene may have relatively milder disease than those less than two copies. The magnitude of benefit with onasemnogene abeparvovec (compared with best supportive care) will be less than for infants with more severe disease; however, the pharmacoeconomic model only considered symptomatic patients. As such, this uncertainty is noted in the recommendation and would require a greater price reduction than the current result of the pharmacoeconomic model to achieve a comparable incremental cost-effectiveness ratio.

Given the natural history of SMA, the available data, and clinical expert opinion CDEC concluded that the observed benefit from a single dose of onasemnogene abeparvovec based on the data from the interim SPR1NT analysis supports reimbursement in patients who are pre-symptomatic and have one to three copies of the SMN2 gene.

Can CDEC confirm agreement with the product monograph recommendation that patients with anti-AAV9 antibody titers higher than 1:50 should not be treated with onasemnogene abeparvovec, or whether a different threshold should be used?

CDEC Response

An exclusion criterion in all of the reviewed studies was an anti-AAV9 antibody titer greater than 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. As such, there is no evidence of the potential efficacy or harms of onasemnogene abeparvovec in this population.

In reference to biallelic mutations of the SMN1 gene, is treatment consideration specific only for those with no SMN1 genes (homozygous deletions) or should there be consideration of treatment for patients who are compound heterozygotes as well? For example, nusinersen (Spinraza) can be reimbursed for patients with compound heterozygous disease.

CDEC Response

The STR1VE-US and START studies included patients with a diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2 (inclusive of the known SMN2 gene modifier mutation (c.859G>C). While eligibility criteria may have included patients with compound heterozygous disease, the exact number of patients with this genetic profile included in the trials was not reported. The clinical experts noted that although it has not been reported what the effects of onasemnogene abeparvovec are by genetic profile (homozygous or compound heterozygous), patients with a deletion and point mutation who present before six months would be expected to have similar course as those whose bi-allelic mutation is homozygous on a biological basis.

In the patient populations for which there is expected benefit with onasemnogene abeparvovec, what outcomes, evaluations and scores, and over what time period, should be used to assess the efficacy and safety of onasemnogene abeparvovec? How would the outcomes and evaluations be different based on age of treatment, symptomatic versus asymptomatic, and number of gene copies.

CDEC Response

CDEC concluded that monitoring for clinical benefit it is not a relevant question for onasemnogene abeparvovec, which is only administered once; unlike medication that require ongoing administration where follow-up is important to determine continuation of funding, this is less important for a one time administration.

Nonetheless, monitoring for clinical response is an important research question that could inform an amendment of the reimbursement recommendation in the future (or may be relevant for consideration of other treatments). Therefore, jurisdictions should consider requesting the sponsor to collect data prospectively to provide evidence in this regard.

Given the unknown durability of treatment effect, how should the participating drug programs evaluate response to therapy when patients age out of the scoring tools that were used in clinical trials, and age out of the scoring tool used to establish their baseline motor function? How should the drug programs transition patients from CHOP-INTEND or HINE to HFMSE while ensuring continued response to treatment?

CDEC Response

Refer to the response for the previous question.

Alternatively, should ongoing treatment effect be evaluated through assessment of only specific motor milestones noted in the trial outcomes (e.g., holding head erect, rolling, ability to sit unsupported)? If so, considering that the existing evidence is in patient populations under 6 months of age, would these same infant/early childhood motor milestones be used to assess the treatment effect as the patient progresses through childhood and beyond? For example, would treatment be considered a success for a 5-year old who can only hold their head up, or should they be expected to have gained other age-related functionality?

CDEC Response

Refer to the response for the previous question.

How soon can a patient treated with onasemnogene abeparvovec (within the different eligible populations) be assessed to determine if therapy has been successful or failed, and what would the indicators of treatment failure be?

CDEC Response

Refer to the response for the previous question.

CDEC noted clinical expert input to the CADTH clinical review report:

> *During the first year of life, treatment response should be assessed approximately every four months for symptomatic patients. Within this assessment frequency, if there were several consecutive visits where the patient has decreased functioning, it can be concluded that the treatment was not effective. In pre-symptomatic patients, treatment response should be assessed approximately every six months. Ideally, these assessments should continue with such frequency until a patient is six years old.*

Primary endpoints used to test the efficacy of onasemnogene abeparvovec in STR1VE-US and SPR1NT were:

- Proportion of infants who achieved functional independent sitting for ≥30 seconds at 18 months of age.
- Survival, defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age.

Can CDEC comment on whether individuals who did not receive nusinersen prior to onasemnogene abeparvovec should be considered for therapy with nusinersen (or another yet-to-become-available SMA-specific therapy) after receiving but not benefiting or have an insufficient response from onasemnogene abeparvovec? What about patients who did receive nusinersen with some response prior to onasemnogene abeparvovec but did not benefit or have insufficient response from onasemnogene abeparvovec?

CDEC Response

There is currently no evidence to inform on the efficacy of simultaneous or sequential administration of therapies indicated for the treatment of SMA.

Would the need to use nusinersen, risdiplam or another SMA therapy after treatment with onasemnogene abeparvovec indicate treatment failure?

CDEC Response

There is currently no evidence to inform this question.

Is there any way for jurisdictions to identify SMA patients with 1 or 2 gene copies who are pre-symptomatic at 6 months of age without newborn screening?

CDEC Response

Clinician input to CDEC noted that newborn screening is the preferred means of identifying these patients. Without newborn screening, clinicians look to identify patients prenatally in families with know carrier states in both parents or if there is a family history of SMA (particularly in siblings).

What does CDEC recommend to jurisdictions with respect to management and treatment of pre-symptomatic patients who are otherwise eligible for onasemnogene abeparvovec, but older than 6 months?

CDEC Response

This population was not included in the reviewed studies. There is no evidence to inform on the effect of onasemnogene abeparvovec this patient group. Generalizability of the results of the SPR1NT study to this patient population is limited for the following reasons:

1. The SPR1NT cohort 1 (2 SMN2 copies) are likely to develop symptoms within the first six months of life
2. While it is unknown how many of the SPR1NT cohort 2 (3 SMN2 copies) would have progressed to exhibit symptoms within the first six months of life, studies have shown that up to 50% of Type 1 SMA (symptoms appear within the first 6 months of life) may have three SMN2 gene copies.
3. Assessment of the efficacy in the SPR1NT study was established at 18 months of age for cohort 1 and at 24 months for cohort 2.

At what time horizon does the cost effectiveness for patients treated with nusinersen equal the cost effectiveness for patients treated with onasemnogene abeparvovec?

CDEC Response

This is a difficult question to answer because the actual price paid by drug plans is unknown.

Using available prices, CADTH estimated that the cumulative cost in patients treated with nusinersen is lower than in patients treated with onasemnogene abeparvovec until 11 years after initial treatment (cumulative costs at year 11 for: nusinersen = $3,371,179; onasemnogene abeparvovec = $3,236,664).

It should be noted that:

1. This includes both the drug acquisition cost and health care costs
2. There is uncertainty in both of these
3. The pharmacoeconomic model was restricted to patients who are symptomatic at baseline (unable to sit unassisted), and with two copies of the SMN2 gene. Results for patients who are asymptomatic or have three copies of the SMN2 gene are unknown.

What is the current duration of treatment effect that is supported by clinical evidence?

CDEC Response

The current treatment effect duration as supported by clinical evidence is the duration of the STR1VE-US study (approximately 30 months). In the CADTH pharmacoeconomic report, a scenario analysis reducing the time horizon to five years was performed, given there is limited data on the long-term efficacy of onasemnogene abeparvovec or nusinersen. The scenario analysis does not align with the length of the STR1VE-US study, and the submitted model was not flexible enough to accommodate a time horizon outside of five-year increments. The results of this analysis were:

Treatment		Total Cost ($)	Total QALYs	ICER ($/QALY)
Five-year time horizon	Best supportive care	137,413	0.481	-
	Onasemnogene abeparvovec	3,098,729	1.514	2,866,859
	Nusinersen	2,034,209	1.383	-
	Onasemnogene abeparvovec	3,098,729	1.514	8,109,261

Given the current evidence, this is essentially unknown and dependent on the duration of efficacy seen in the studies. It is difficult to provide a true duration of effect with confidence because not all patients respond to treatment and it is unclear if early responders have relapses or become poor responders.

November 18, 2020 Meeting (Initial)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None

March 17, 2021 Meeting (Reconsideration and Clarification)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None