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CADTH Reimbursement Recommendation

Risdiplam (Evrysdi)

Indication: For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older

Sponsor: Hoffmann-La Roche Ltd.

Final Recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Evrysdi (Risdiplam)?

CADTH recommends that Evrysdi should be reimbursed by public drug plans for the treatment of spinal muscular atrophy (SMA) in patients aged 2 months and older, if certain conditions are met.

What Are the Conditions for Reimbursement?

Evrysdi should only be reimbursed if the patient is under the care of a specialist with experience in the diagnosis and management of SMA, it is not used in combination with nusinersen or onasemnogene abeparvovec, and the price is reduced.

Which Patients Are Eligible for Coverage?

Evrysdi should only be reimbursed to treat patients aged 2 months to 7 months with genetic documentation of 2 or 3 copies of the survival motor neuron 2 (*SMN2*) gene or non-ambulatory patients aged 8 months to 25 years with genetic documentation of 2 or 3 copies of the *SMN2* gene. Patients are ineligible if they currently require permanent invasive ventilation. After 12 months of treatment, patients should be assessed to ensure clinical benefit.

Why Did CADTH Make This Recommendation?

- In 1 trial in SMA patients aged 2 months to 7 months, treatment with Evrysdi improved survival and the achievement of motor milestones versus a historical control group. In another in SMA patients aged 2 years to 25 years, Evrysdi improved motor function versus placebo.
- Evrysdi should be priced no higher than Spinraza because of uncertainty about the relative cost-effectiveness in infants. For those diagnosed after infancy, Evrysdi was not cost-effective compared with best supportive care even after a substantial price reduction.
- Based on public list prices, the 3-year budget impact is more than $87 million.

Additional Information

What is Spinal Muscular Atrophy?

SMA is a severe neuromuscular disease, with an incidence of 1 in 10,000 live births, and the leading genetic cause of infant death. The root cause is SMN protein deficiency (usually from *SMN1* mutation). SMN protein is essential for motor neuron survival; deficiency weakens the muscles and leads to debilitation. A younger age at symptom onset and fewer *SMN2* genes (which can express some SMN protein) increase the severity of the disease.

Unmet Needs in SMA

There are 2 other approved treatments for SMA in Canada (Zolgensma and Spinraza). However, some patients may not respond to these medications. No treatment can reverse any neurological damage that has already occurred due to SMA.

How Much Does Evrysdi Cost?

Treatment with Evrysdi is expected to cost approximately $93,456 per patient annually in patients between 2 months to 24 months of age, and $335,415 to $354,000 per patient annually in patients older than 24 months.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that risdiplam should be reimbursed for the treatment of spinal muscular atrophy (SMA) in patients aged 2 months and older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, single-arm study, FIREFISH Part 2 (N = 41), enrolled infants with SMA who were aged 2 months to 7 months with symptom onset before 3 months. Patients were required to have 2 copies of the survival motor neuron 2 (*SMN2*) gene and not be receiving permanent ventilation. The primary outcome of the FIREFISH Part 2 study was the proportion of infants able to sit without support after 12 months on treatment. After 12 months, 29.3% of patients who received risdiplam were able to sit without support compared with the natural history threshold of 5% (P < 0.0001). Patients in the study who received risdiplam also demonstrated improved motor and developmental milestones compared with pre-specified performance thresholds using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Hammersmith Infant Neurological Examination (HINE) Section 2 scales. In addition, 85.4% of patients who received risdiplam were alive and did not require permanent ventilation at month 12 compared with a predefined threshold of 42% (P < 0.0001).

One phase III, double-blind, placebo-controlled study, SUNFISH Part 2 (N = 180), enrolled non-ambulatory patients with SMA aged 2 years to 25 years. Most enrolled patients had 3 *SMN2* gene copies (89.2% in the risdiplam group, 83.3% in the placebo group). At baseline, 10.8% of patients in the risdiplam arm and 10.0% in the placebo arm were able to stand. Patients in the SUNFISH Part 2 study who received risdiplam had an improvement in motor function from baseline to month 12 with a mean difference versus placebo of 1.55 points (95% CI, 0.30 to 2.81; P = 0.0156) in the 32-Item Motor Function Measure (MFM32) score. Overall, 38.3% of patients in the risdiplam arm were considered responders on the MFM32 (change of 3 points or more from baseline) compared with 23.7% in the placebo group (odds ratio [OR] = 2.35; 95% CI, 1.01 to 5.44; P = 0.0469). Patients who received risdiplam also had statistically significantly improved upper limb mobility versus placebo based on the change in Revised Upper Limb Module (RULM) score (mean difference = 1.59 points; 95% CI, 0.55 to 2.62; P = 0.0028).

The CADTH reanalysis of the sponsor-submitted cost-utility model estimated the incremental cost-effectiveness ratio (ICER) of risdiplam compared with best supportive care (BSC) to be $1,203,108 per quality-adjusted life-year (QALY) in patients with SMA type 1, and $37,378,163 per QALY in patients with SMA type 2 or 3. Risdiplam was less costly than nusinersen, and the sponsor assumed equivalent efficacy between treatments. However, the lack of long-term comparative efficacy evidence means that the incremental effectiveness, and thus cost-effectiveness, of risdiplam compared with nusinersen is highly uncertain.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Genetic documentation of 5q SMA homozygous gene deletion or compound heterozygote.	Consistent with diagnostic criteria for SMA used in the main trials, FIREFISH Part 2 and SUNFISH Part 2.
2. Patients who are symptomatic and either: 2.1. aged between 2 months and 7 months (inclusive) and have genetic documentation of 2 or 3 copies of the *SMN2* gene 2.2. aged 8 months up to 25 years, are non-ambulatory, and have genetic documentation of 2 or 3 copies of the *SMN2* gene.	FIREFISH Part 2 demonstrated meaningful clinical benefit in motor function in patients with the characteristics described in Condition 2.1. SUNFISH Part 2 demonstrated a benefit in motor function in patients aged 2 years to 25 years who were non-ambulatory. The benefit is likely to be clinically meaningful for some patients, although it is not possible to identify these patients before initiation of therapy with risdiplam.
3. Patient does not currently require permanent invasive ventilation.	There is no evidence to suggest a benefit in patients who reach an advanced state of SMA where permanent ventilation is required.
4. The maximum duration of initial authorization is 12 months.	Assessment of benefit from treatment with risdiplam occurred at 12 months in both trials. Authorization of funding for 12 months provides flexibility to accommodate the practical challenges of assessing clinical response after treatment initiation given the natural history of SMA.
Discontinuation	
5. Reimbursement of treatment with risdiplam should be discontinued if any of the following occur: 5.1. there is no demonstrated achievement in, or maintenance of, motor milestone function (as assessed using an age-appropriate measurement) after treatment initiation in patients aged between 2 months and 2 years at the time of treatment initiation 5.2. there is no demonstrated maintenance of motor function (as assessed using an age-appropriate measurement) after treatment initiation in patients aged between 2 years and 25 years at the time of treatment initiation 5.3. permanent invasive ventilation is required.	Results from FIREFISH Part 2 and SUNFISH Part 2 indicated that only some patients will respond to therapy.
6. The decision to discontinue reimbursement should be based on 2 assessments separated by no longer than a 12-week interval, each done within 6 weeks of the annual renewal date.	This provides flexibility to accommodate the practical challenges of assessing clinical response to treatment given the natural history of SMA and variation in individual patient performance on functional tests used to assess response.
Prescribing	
7. Patient must be under the care of a specialist with experience in the diagnosis and management of SMA.	The diagnosis and treatment of SMA requires specialist medical care.
8. Risdiplam should not be used in combination with nusinersen or onasemnogene abeparvovec.	There is no evidence to support combination therapy.

Reimbursement condition	Reason
Pricing	
9. A reduction in price.	The cost-effectiveness of risdiplam compared with nusinersen is highly uncertain for SMA type 1. There is no evidence to suggest risdiplam should be priced higher than nusinersen. A price reduction of 99% for SMA type 2 and 3 patients still resulted in very high ICER estimates in comparison with BSC.

BSC = best supportive care; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.

Implementation Guidance

1. CDEC heard from clinical experts that functional testing may demonstrate considerable variation between different visits. As such, evaluation for determining discontinuation should be based on the best performance over at least 2 assessments, separated by no longer than a 12-week interval and excluding intercurrent illnesses.
2. Permanent ventilation was defined in the included studies as the need for a tracheostomy or requirement of 16 hours or more of non-invasive ventilation (e.g., BiPAP) per day or intubation for more than 21 consecutive days in the absence of, or following the resolution of, an acute reversible event.
3. *Non-ambulatory* may be defined, per the SUNFISH Part 2 study, as an inability to walk unassisted (i.e., without braces; assistive devices such as canes, crutches, or calipers; or personal or hand-held assistance) for 10 m or more at the time of treatment initiation.
4. Given the extraordinarily high cost of risdiplam, the budget impact of using risdiplam will be considerable, even if the price is reduced substantially. Therefore, the reimbursement conditions reflect the importance to CDEC of identifying those patients with SMA who are most likely to benefit from treatment. CDEC noted that risdiplam was expected to reduce budget impact among SMA type 1 patients, but greatly increase the overall drug budget among the full indicated population.
5. Sequencing of risdiplam relative to other medications indicated for the treatment of SMA is an important evidence gap. CDEC noted that patients who have been receiving nusinersen for SMA (which is administered intrathecally, a difficult and invasive mode of administration that has potential for related adverse events) and who meet the initiation conditions above should not be precluded from receiving reimbursement of treatment with risdiplam. CDEC also noted that for patients who have received onasemnogene abeparvovec, no further treatment with other medications indicated for treatment of SMA should be reimbursed, including risdiplam, based on currently available evidence.
6. Functional assessment tools for patients with symptom onset before 2 years of age could include the HINE Section 2. The clinical experts recommended the HINE Section 2 for assessment of infants.
7. Functional assessment tools for patients 2 years and older could include the Hammersmith Functional Motor Scale Expanded (HFMSE). Patients who cannot be assessed by the HFMSE should be assessed with another appropriate tool. The clinical

experts recommended the HFMSE and RULM scales for non-ambulatory older patients (not infants).

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 and onasemnogene abeparvovec are currently the only approved drug treatments for patients with SMA. Despite the availability of these 2 agents, 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 3 months and uncertainty that the intended dose consistently reaches the site of action, which could lead to progressive bulbar muscle weakness in some patients. CDEC discussed that the different routes of administration for risdiplam and nusinersen may inform patient preference and the practicality of treatment. CDEC also noted that onasemnogene abeparvovec is not indicated in patients who have later-onset SMA or high titres of antibodies to the adeno-associated virus capsid vector.
- CDEC identified numerous limitations associated with the single-arm trial design of the FIREFISH Part 2 study. Although CDEC considered the observed treatment effects of risdiplam on assessed outcomes in the study to be clinically meaningful, the lack of a concurrent control group precluded a precise estimation of the magnitude of benefit.
- CDEC identified several limitations associated with the double-blind, placebo-controlled SUNFISH Part 2 trial. Most importantly, there were uncertainties whether the observed benefit of risdiplam was clinically meaningful and whether any efficacy is expected in adolescent and adult patients. CDEC noted that the magnitude of benefit with risdiplam in adolescent and adult patients, especially in patients aged 18 years to 25 years, may be smaller than in younger patients.
- CDEC discussed the challenge of recommending reimbursement criteria for risdiplam based on SMA subtype (i.e., SMA type I, II, III, or IV) considering there is overlap between SMA subtypes on some criteria, and that the achievement of major motor milestones, such as sitting or walking independently, is both a goal of treatment and a criterion used for classifying patients. In addition, with the availability of disease-modifying therapies, these classifications are likely to become obsolete as patients show symptoms consistent with 1 classification but achieve motor milestones that are consistent with a potentially better classification.
- CDEC noted the following:
    - FIREFISH Part 2 included only children aged up to 210 days (7 months) and the SUNFISH Part 2 study included only patients aged 2 years to 25 years
    - FIREFISH Part 2 included only patients who had 2 copies of the *SMN2* gene.
- There is a lack of evidence in patients with SMA with symptom onset between 7 months and 2 years of age and in patients with symptom onset early in life and who have 3 copies of the *SMN2* gene. However, CDEC concluded that these limitations in the designs of the studies should not exclude these patients from the reimbursement population for risdiplam.

- Patient and clinician input noted that preventing mobility loss is clinically important in patients with SMA who can walk. Patients who were ambulatory or non-ambulatory were eligible for participation in the SUNFISH Part 1 study, whereas patients who were ambulatory were excluded from the SUNFISH Part 2 study. Part 1 of the SUNFISH study included 7 patients (13.7%) who were ambulatory at baseline and Part 2 included 4 patients (3 treated with risdiplam and 1 treated with placebo) who were ambulatory at baseline, despite not being eligible for enrolment. However, neither part of the SUNFISH study was designed to statistically evaluate outcomes in this subgroup of patients. CDEC identified this evidence gap caused by the small sample sizes of ambulatory patients and the statistical design of the SUNFISH study and could not determine the treatment effects with risdiplam in patients who are ambulatory at the start of treatment.
- There is an absence of efficacy data in patients older than 25 years of age at the time of initiating treatment. CDEC noted that a subgroup analysis in the SUNFISH Part 2 study suggested there was lower efficacy in patients 18 years to 25 years of age compared with other age groups. The maximum age of study participants at treatment initiation in the SUNFISH Part 2 study was 25 years. CDEC also noted that the JEWELFISH study, an ongoing study to evaluate the safety of risdiplam in previously treated SMA patients aged 6 months to 60 years, will be the first study to provide efficacy data for risdiplam in patients initiating treatment after the age of 25 years.
- Unlike nusinersen and onasemnogene abeparvovec, risdiplam is currently not approved for use in patients younger than 2 months of age. This includes pre-symptomatic patients identified through newborn screening. CDEC noted that studies are undergoing for the effects of risdiplam in this subpopulation.

Background

Risdiplam has a Health Canada indication for the treatment of SMA in patients aged 2 months and older. The product monograph reports that there are limited data on risdiplam for patients older than 25 years of age. Risdiplam is a *SMN2* pre-mRNA splicing modifier. Risdiplam corrects the splicing of *SMN2* to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels. Risdiplam is available as a dry powder that must be reconstituted to an oral solution by a health care provider before being dispensed. Risdiplam is administered once daily after a meal at approximately the same time each day. The dosage of risdiplam is determined by age and weight as follows:

- age 2 months to less than 2 years: 0.20 mg/kg
- age 2 years or older and less than 20 kg of body weight: 0.25 mg/kg
- age 2 years and older and 20 kg or more of body weight: 5 mg

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a systematic review that included 1 single-arm, uncontrolled trial and 1 randomized controlled trial
- patients' perspectives gathered by 2 patient groups: Muscular Dystrophy Canada (MDC) and Cure SMA Canada (CSMAC)
- input from 6 clinical specialists with expertise diagnosing and treating patients with SMA
- input from 1 clinician group: Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Two patient input submissions for this review were from MDC and CSMAC. These submissions were based on semi-structured interviews, virtual interviews, a focus group of 5 adult patients and 8 parent caregivers, and a survey of patients and caregivers that gathered 96 responses. All respondents lived in Canada, and all data were collected between October 2020 and December 2020.

Six main themes were apparent from the patient input submissions (listed in order of frequency reported): (1) enormous impact on activities of daily living; (2) effects on breathing, swallowing, and mobility; (3) significant dependence on caregiving supports; (4) loss of independence and control; (5) pain, age-related fatigue, and mental health; and (6) fear of falling.

Some of the major health concerns expressed by both patient groups included: respiratory function (and illnesses like pneumonia); muscle strength, fine motor skills, falls, and safety; nutrition (inability or losing ability to chew and swallow); voice and speech; mental and emotional health; and being easily fatigued. Transportation time and distance combined with accessibility when out in public were noted as important considerations in day-to-day life. The desire to maintain, or regain, independence for as long as possible was common among the responses, as was the constant fear of progressive loss of function and declining health. Living with SMA requires additional therapy, many medical appointments, and a high degree of dependence on caregivers and equipment, all of which lead to exhaustion for both patients and caregivers as well as increased strain on mental health and relationships.

Many patients who contributed to the patient group input were receiving nusinersen. Although they were positive about its therapeutic impact, they described challenges with the treatment, including the intrathecal administration, the costs and disruption of travel, the possibility of hospitalization, and the side effects experienced after a lumbar puncture. Respondents were aware of risdiplam, and felt that a daily, oral treatment would have a positive impact on their lives if it meant fewer hospital visits, less strain on hospital resources and staff, was convenient and easily accessible, and would allow patients and families to have stable careers, education, and family lives. Both patient groups also noted that access to new disease-modifying therapies is variable across Canada and there are still many patients who would benefit from such therapies but do not yet have access to them.

Clinical Evidence

Clinical Trials

The systematic review included 1 single-arm uncontrolled trial and 1 randomized controlled trial.

The FIREFISH Part 2 study (N = 41) is an ongoing, open-label, single-arm, phase III trial investigating the efficacy and safety of risdiplam after 12 months of treatment in infants with 2 copies of the *SMN2* gene (categorized by the investigators as having SMA type I), a body weight greater than the third percentile for age, and not receiving invasive ventilation. A total of 41 infants received risdiplam at an age-determined dose. These infants had an average age of 5.2 months (standard deviation [SD] = 1.47), had onset of symptoms reported at a mean age of 1.64 months (SD = 0.70), and a mean disease duration of 3.59 months (SD = 1.35). At baseline, 4.9% of the infants were able to keep their head upright, while 85.4% did not demonstrate any motor milestone achievement and 70.7% did not require any form of ventilatory support.

The SUNFISH Part 2 study (N = 180) is an ongoing, double-blind, placebo-controlled, phase III trial investigating the efficacy and safety of risdiplam after 12 months of treatment in patients aged 2 years to 25 years (inclusive) who are non-ambulatory. Patients were randomized (2:1 ratio) to receive risdiplam or placebo. The mean age of enrolled patients was 9.9 years (SD = 5.8) in the risdiplam group and 10.3 years (SD = 6.1) in the placebo group. The fewest number of patients were in the 18-year to 25-year age group (11.7% in risdiplam, 13.3% in placebo), followed by the 12-year to 17-year age group (25.0% in risdiplam, 26.7% in placebo). Most patients had 3 *SMN2* gene copies (89.2% in risdiplam, 83.3% in placebo) and more than two-thirds were diagnosed by investigators as having SMA type 2 (70.0% in risdiplam, 73.3% in placebo). At baseline, 10.8% of patients in the risdiplam group and 10.0% in the placebo group were able to stand.

Key limitations of the FIREFISH Part 2 study included:

- The absence of a concurrent control arm in the form of a placebo control or an active control. This increases the risk of overestimating the treatment effect for risdiplam 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.
- The patient population was highly selective. The study did not include children younger than 2 months or older than 6 months, or who had 3 copies of the *SMN2* gene. Therefore, there are no data to directly inform the extent of the effects of risdiplam for these patients.

Key limitations of the SUNFISH Part 2 study included:

- Adult patients with SMA were included in the SUNFISH Part 2 trial; however, they represented the smallest age group in the study (a total of 12.2%). The design of the study, including the outcome measures and duration, was likely not the most appropriate to evaluate the effects of risdiplam in this age group of patients with SMA whose disease progression may be different from younger patients with SMA. Therefore, the generalizability of the overall results is lowest in the 18-year to 25-year age group.
- The SUNFISH Part 2 study excluded ambulatory patients. Considering the nature of SMA, where alpha motor neurons are irreversibly lost as disease progresses, patients with higher

motor function may have a greater number of alpha motor neurons than patients who have lost such motor functions. Therefore, ambulatory patients may exhibit a different response than non-ambulatory patients, so the generalizability of the SUNFISH Part 2 results to this patient population is unclear.

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 primary outcome in the FIREFISH Part 2 study was sitting without support for 5 seconds after 12 months of treatment as assessed by the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) tool. Other key secondary outcomes included in a statistical testing hierarchy were the proportion of patients who achieved a CHOP INTEND score of 40 or higher at month 12, the proportion of patients who achieved an increase of at least 4 points from baseline on the CHOP INTEND at month 12, the proportion of motor milestone responders as assessed by the HINE Section 2 at month 12, the proportion of patients alive without permanent ventilation at month 12, and the proportion of patients sitting without support for 30 seconds (item 26 of BSID-III) at month 24. No minimum important difference (MID) was identified for the BSID-III total score or for the CHOP INTEND total score, while the HINE Section 2 had an estimated MID of greater than 1 point.

The primary outcome in the SUNFISH Part 2 study was the change from baseline in the MFM32 score at month 12. Key secondary outcomes within the statistical testing hierarchy were the proportion of patients with a change from baseline in the MFM32 total score of 3 or more at month 12, in the total score of the RULM at month 12, in the total score of the HFMSE at month 12, in forced vital capacity (FVC) at month 12, in caregiver-reported SMA Independence Scale (SMAIS) total score at month 12 as well as the proportion of individuals rated as "improved" on the clinician-reported global impression of change (CGI-C) at month 12. The sponsor proposed that a difference of 3 points or more on the MFM32 may indicate the acquisition of a new function or the improvement of several functions. The RULM has an estimated MID of 2.9 points, the HFMSE has an estimated MID of more than 2 points, and the SMAIS has an estimated MID of 1 to 5 points. No MIDs were identified for the other outcomes.

Efficacy

In the FIREFISH Part 2 study, 29.3% of infants were able to sit without support after 12 months on treatment. This was contrasted with a natural history threshold of 5% ($P < 0.0001$). Of the reported secondary outcomes that were within the statistical testing hierarchy (at 12 months of treatment), 56.1% of infants had a CHOP INTEND score of 40 or higher ($P < 0.0001$ against a performance criterion of 17%), 90.2% achieved an increase of at least 4 points in the CHOP INTEND score from baseline ($P < 0.0001$ against a performance criterion of 17%), and 78.0% were considered motor milestone responders assessed through the HINE Section 2 ($P < 0.0001$ against a performance criterion of 12%). At month 12, 85.4% of patients were

alive and did not require permanent ventilation, which was statistically significant compared with a predefined natural history threshold of 42% (P < 0.0001).

Motor function improved in patients who received risdiplam in the SUNFISH Part 2 study, with a mean difference versus placebo of 1.55 points (95% CI, 0.30 to 2.81; P = 0.0156) for the change from baseline on the MFM32 score. The first secondary outcome tested within the statistical testing hierarchy after the primary outcome was the MFM32 responders (change of 3 points or more from baseline). This outcome showed that 38.3% of patients in the risdiplam group were considered responders, compared with 23.7% in the placebo group (OR = 2.35; 95% CI, 1.01 to 5.44; P = 0.0469). Then the change in the RULM score was tested, with a mean difference versus placebo of 1.59 points (95% CI, 0.55 to 2.62; P = 0.0028) in favour of risdiplam. The next 2 co-outcomes tested, the change from baseline in the total score of HFMSE and the change from baseline in best percentage predicted value FVC, failed to achieve statistical significance. Patient and clinician-reported outcomes, measured through the SMAIS and CGI-C tools, were next on the statistical testing hierarchy; however, because the previous outcomes failed to achieve statistical significance, no additional statistical testing could be performed based on the pre-specified analysis plan.

Harms (Safety)

In the FIREFISH Part 2 study, at least 1 adverse event was reported in all enrolled infants. Upper respiratory tract infection was the most commonly reported adverse event (46.3%), followed by pneumonia (39.0%), pyrexia (39.0%), and constipation (19.5%). Serious adverse events were reported in 58.5% of the infants (24 of 41), with most related to respiratory problems or respiratory infections. Three infants died during the study; 2 deaths were attributed to pneumonia and 1 to respiratory failure.

In the SUNFISH Part 2 study, at least 1 adverse event was reported in 92.5% and 91.7% of enrolled patients in the risdiplam and placebo arms, respectively. Upper respiratory tract infection was the most commonly reported adverse event (31.7% in risdiplam, 30.0% in placebo), followed by nasopharyngitis (25.8% in risdiplam arm, 25.0% in the placebo arm), pyrexia (20.8% in risdiplam arm, 16.7% in placebo arm), and headache (20.0% in risdiplam arm, 16.7% in placebo arm). Serious adverse events were reported in 20.0% of patients who received risdiplam and 18.3% in patients who received placebo. Most of the serious adverse events were related to respiratory problems or respiratory infections.

Indirect Evidence

One sponsor-submitted indirect treatment comparison (ITC) was reviewed. The ITC compared risdiplam to nusinersen in 2 distinct patient populations: infantile-onset SMA (classified as SMA type 1) and later-onset SMA (classified as SMA type 2 or 3). An unanchored matched-adjusted indirect comparison (MAIC) was performed for the SMA type 1 population and included pooled subgroup data from Part 1 and Part 2 of the FIREFISH study for risdiplam and the ENDEAR study for nusinersen. The results of the SMA type 1 unanchored MAIC suggest a hazard ratio for ventilation-free survival of risdiplam versus nusinersen of 0.20 (95% CI, 0.06 to 0.42) and an overall survival hazard ratio of 0.26 (95% CI, 0.03 to 0.66). Motor function assessment using the HINE Section 2 showed favourable results for risdiplam in the outcomes of motor milestone response, full head control, and sitting without support, while the outcome of rolling was favourable in the direction of nusinersen. Two outcomes, sitting with or without support and standing, did not show a clear direction. However, important limitations, including poor statistical robustness in the data for many of the comparisons and the low likelihood that the assumption that all known and unknown effect modifiers

and prognostic factors were accounted for within the model was met, means there is considerable uncertainty regarding the actual observed effect that is attributed to risdiplam.

An anchored MAIC was used for later-onset SMA and included the SUNFISH study for risdiplam and the CHERISH study for nusinersen, with the placebo arm in SUNFISH and the sham arm in CHERISH acting as a common comparator. Due to large discrepancies in the inclusion and exclusion criteria between the studies, the ITC only used a subset of patients from the SUNFISH Part 2 study that would have been included in the CHERISH study, reducing the sample size of the SUNFISH Part 2 study by 62% and breaking randomization. The sample sizes were further reduced to make the populations more homogeneous; the resulting effective sample size was too small to provide a robust analysis, as reflected by very wide confidence intervals. No concrete conclusions could be drawn from the results of this analysis.

Economic Evidence

Cost and Cost-Effectiveness

At a cost of $193.9725 per mg, the daily cost for patients 2 years of age and older (and 20 kg and over) is $970, for a total annual cost of $354,000. The average daily cost and annual cost for patients who are between 2 months and 2 years of age are $256 and $93,456, respectively.

The sponsor submitted a cost-utility analysis that assessed risdiplam compared with nusinersen and BSC, defined as care provided in the absence of disease-modifying treatment, for the treatment of SMA. The sponsor submitted 2 models to address this target population. One model was for patients with SMA type 1, often referred to as infantile-onset SMA. The second model was for patients with SMA type 2 or 3, for whom onset typically occurs after 18 months or further into childhood or adolescence. The 2 models were considered to better reflect the different natural history, age of onset, baseline motor function, and treatment efficacy between these 2 populations. Both model structures were based on motor function milestone achievement. The submitted models reported both QALYs and life-years over a lifetime time horizon of 25 years in the SMA type 1 population and 80 years in the SMA type 2 or 3 population. The base case analyses were conducted from the perspective of the Canadian public health care payer.

In SMA type 1, the FIREFISH study informed treatment efficacy with risdiplam; the ENDEAR study informed an unanchored MAIC for risdiplam with BSC. For SMA type 2 or 3, the SUNFISH study informed transitions between motor function health states for risdiplam and BSC. In both subgroups, the sponsor assumed equivalent treatment efficacy (motor function milestones, overall survival, and event-free survival) for risdiplam and nusinersen.

CADTH identified the following key limitations with the sponsor's submission:

- In the absence of direct comparative information, the magnitude of clinical benefit, with regards to motor milestone achievement and survival (i.e., mortality and requirement of permanent ventilation), of risdiplam compared with BSC or nusinersen is highly uncertain.

Further, the lack of long-term comparative efficacy of risdiplam or nusinersen adds to the extent of clinical uncertainty. It is not clear if they are equally effective.

- The sponsor's base cases included health state utilities for 2 informal caregivers per patient in addition to patient health state utilities. Although CADTH acknowledges that caregiver burden is significant with SMA, defining health state utilities in this manner does not align with CADTH requirements for drug submissions. The inclusion of a non-patient utility overestimated the total QALY benefits observed with risdiplam.
- The submitted model structures and associated assumptions may not appropriately capture all key changes in patient quality of life, including SMA-related developments such as the requirement of nutritional support or loss in functional status.
- The sponsor's model assumed that mortality was independent from illness severity, with identical mortality rates for all patients. This assumption is not appropriate because patients would have different mortality based on their motor, respiratory, and bulbar function. This contributed meaningful uncertainty to the results.

In a reanalysis, CADTH removed caregiver utilities. CADTH could not address the remaining key limitations, including limitations with the submitted model structure and the comparative efficacy of risdiplam with nusinersen and BSC. Interpretations of the estimated mean ICER and price reduction should take the resulting uncertainty into account.

Compared with BSC, risdiplam is associated with an ICER of greater than $1.2 million per QALY in SMA type 1 and an ICER greater than $37 million in SMA type 2 or 3. Risdiplam is not considered cost-effective at a conventional willingness-to-pay threshold. Price reductions of 99% would not be sufficient to reach a $50,000 per QALY threshold in either subgroup. Given the assumption of equivalent treatment efficacy, risdiplam continued to dominate nusinersen in reanalysis due to the drug acquisition costs associated with risdiplam being less than the publicly available price of nusinersen.

Budget Impact

The sponsor estimated that the 3-year budget impact of risdiplam would be $77,420,166. CADTH noted that the sponsor's analysis underestimated the proportion of patients with SMA type 1 currently receiving treatment, underestimated the likely rate of treatment retention for risdiplam, and made assumptions about the proportion of patients covered under public plans that may not reflect reality. After accounting for these limitations, CADTH estimated a 3-year budget impact of $87,744,812 ($30,183,701 in year 1, $29,146,849 in year 2, and $28,414,263 in year 3). CADTH noted that risdiplam was expected to cost saving among patients with SMA type 1 (i.e., risdiplam cost saving), but this reduction was outweighed by the additional cost among patients with SMA type 2 and 3.

Members of the Canadian Drug Expert Committee

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.

Initial meeting date: April 21, 2021

Regrets: One committee member did not attend

Conflicts of interest: None

Reconsideration meeting date: July 21, 2021

Regrets: None

Conflicts of interest: None