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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Edaravone (RADICAVA)

(Mitsubishi Tanabe Pharma Corporation)

Indication: For the treatment of Amyotrophic Lateral Sclerosis (ALS)

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Abbreviations

ALS	amyotrophic lateral sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised
CNS	central nervous system
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Edaravone (Radicava) 60 mg intravenous infusion
Study Question	What is the incremental cost-effectiveness of edaravone for the treatment of ALS compared with standard of care in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with ALS
Treatment	Edaravone
Outcomes	• Lifetime discounted costs • LYs • QALYs
Comparator	Standard of care (with 85% receiving riluzole)
Perspective	Canadian public health care payer
Time Horizon	20 years (lifetime)
Results for Base Case	ICUR = $1,957,200 per QALY gained
Key Limitations	• Model structure does not reflect the clinical pathway of ALS: patient transitions from stage 1 to stage 3, stage 1 to stage 4A, stage 1 to stage 4B, stage 2 to stage 4A, or stage 2 to stage 4B were not possible. These transitions are important in order to accurately capture the natural history of ALS because functional involvement of all three regions is not required prior to moving into a model advanced health state (stages 4A and 4B). • Important patient characteristics (including patient age, gender, site of onset, and progression rate prior to diagnosis) were not described or were varied in scenario analyses. Sensitivity analysis did not explore the heterogeneity in disease-progression rates associated with these patient characteristics. Patient characteristics are likely to reflect the ICUR. • Treatment effect was assumed to be constant across ALS clinical stages. This is inconsistent with: the physiological mechanism of delayed progression through the inhibition of motor-neuron death; the results stratified by Japanese ALS severity level in Trial 19 (which indicated more limited treatment benefit in patients in higher-severity stages of ALS); and with the results in Study 18 which found no treatment benefit in the trial population (patients at higher-severity stages of ALS). • Non-drug ALS stage–specific health care costs were substantially greater than the reported costs in the literature. • Drug administration costs were not fully accounted for. • The cost-effectiveness analysis was performed for a cohort of patients with a distribution of disease severities. In order to better inform decision-making, the cost-effectiveness analysis should have been performed for groups of patients who were distinguishable on personal or clinical characteristics at the time the treatment decision was made.

CDR Estimate(s)	• CDR reanalysis of the manufacturer's base case addressed major limitations including: changes to the ALS natural history transitions, enabling progressive transitions to non-adjacent health states; using a hazard rate–ratio approach for estimating the effectiveness of edaravone; revised costs for drug administration; and revised costs for non-drug ALS stage–stratified health care.
	• In addition, CDR reanalysis were stratified by the initial stage of disease and explored uncertainty in disease-progression rates and treatment effectiveness by disease stage through sensitivity analysis.
	• The ICUR for edaravone compared with the current standard of care, when treating patients in:
	  ○ stage 1: $1,441,000 per QALY gained
	  ○ stage 2: $1,937,000 per QALY gained
	  ○ stage 3: $3,152,000 per QALY gained
	  ○ stage 4A: $2,785,000 per QALY gained.
	• The key variables identified in sensitivity analysis were: treatment effectiveness of edaravone by stage of disease; application of treatment-stopping rules; and, the cost of treatment.

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.

Drug	Edaravone (Radicava)
Indication	For the treatment of amyotrophic lateral sclerosis (ALS)
Reimbursement Request	As per indication
Dosage Form(s)	Intravenous solution, 30 mg/100 mL per infusion bag
NOC Date	October 3, 2018
Manufacturer	Mitsubishi Tanabe Pharma Corporation

Executive Summary

Background

Edaravone (Radicava) is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS).[1] Edaravone is available as a 30 mg/100 mL solution for infusion. It is administered intravenously as 60 mg infusions over 60 minutes daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. In the first month of treatment, edaravone is administered for 14 days (rather than 10). The submitted price is $1,424 per 60 mg, or $1,424 per patient daily and $185,182 per patient annually ($190,880 in the first year of treatment).[2]

The manufacturer submitted a cost-effectiveness analysis based on a Markov state–transition model comparing current standard of care (interdisciplinary supportive care plus riluzole) with edaravone plus current standard of care.[3] In standard of care, 85% of patients were concurrently taking riluzole, the only disease-modifying treatment currently available for ALS. The manufacturer assumed that all patients, at any stage of the disease, were eligible for edaravone therapy and that edaravone slowed disease progression at all stages of the disease. The model did not assume a direct treatment effect on disease-specific mortality. The analysis was run over a 20-year time horizon using a three-month cycle length. The analysis adopted a Canadian public health care system perspective.

The manufacturer's analysis indicated that edaravone is not cost-effective compared with standard of care, with an incremental cost-effectiveness ratio of $1,957,200 per quality-adjusted life-year (QALY) gained.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the manufacturer's economic model and analysis, which had the potential for a direct impact on the estimates of the cost-effectiveness of edaravone.

The manufacturer's analysis considered a cohort of patients with various disease-severity levels at treatment initiation, which averaged the cost-effectiveness of treatment with edaravone across different patient groups. Further, other patient characteristics such as age of onset, region of onset, gender, and age were not described for the initial patient cohort;

and, how these features affect disease progression (i.e., differential rates of disease progression) were not explored in the sensitivity analysis. Based on CADTH's current guidelines for economic evaluations,[4] it is recommended that analyses be stratified where disease progression or treatment effect may vary to inform decision-making.

Importantly, the manufacturer's model does not permit disease progression to non-adjacent states (i.e., progression from stage 1 to stages 3 or 4A) which is inconsistent with the natural history of the disease. This is a key limitation, as the model does not accurately capture the progression of ALS and, as such, may provide inaccurate results.

The manufacturer assumed that edaravone is equally effective at reducing disease progression rate at all stages of the disease. This is inconsistent with the proposed mechanism of action and the available clinical evidence stratified by disease severity, which suggest greater progression benefit for patients in earlier stages of ALS. This further highlights the importance of conducting stratified analyses.

The manufacturer's analysis included the costs of only twelve 28-day treatment cycles per year; however, there are thirteen 28-day cycles per year. This results in underestimating the treatment cost by $14,245 per year.

The manufacturer's analysis assumed little to no costs associated with drug administration. For patients living at home, [redacted]. For patients living in a health care facility, the manufacturer did not consider the opportunity cost of nursing time to administer the drug. Any administration cost borne by the public payer will increase the incremental cost-utility ratio (ICUR) for edaravone.

The manufacturer's analysis assumed substantially higher health care costs by ALS disease stage than have been reported in the literature. The estimates used by the manufacturer do not appear to reflect the Canadian setting.

The CDR reanalysis addressed all of the preceding concerns. CDR's modifications to the manufacturer's model included: changing the ALS natural history transitions to enable progressive transitions to non-adjacent health states; using a constant hazard rate and hazard rate–ratio approach for estimating the clinical effectiveness of edaravone; incorporating the costs of one additional treatment cycle per year; revising the costs for the administration of edaravone; and revising the costs for non-drug ALS stage–stratified health care. The CDR reanalysis also explored uncertainty in disease progression and mortality rates to gain insight into how patient heterogeneity might affect the cost-effectiveness of edaravone compared with standard of care. A sensitivity analysis was also performed to explore the potential impacts of differential treatment effectiveness by disease stage, the stopping rules for edaravone after disease progression, and the annual cost of edaravone.

CDR found that, when compared with current standard of care, edaravone treatment increases life expectancy by two to five months and increases quality-adjusted life expectancy by one to three months. However, edaravone treatment increases lifetime health care costs by $200,000 to $385,000 per patient. As a result, the ICUR of edaravone compared with standard of care ranges from $1,441,000 per QALY gained in patients with stage 1 ALS to $3,152,000 per QALY gained in patients with stage 3 ALS. A 95% price reduction is required to reduce the ICUR to less than $200,000 per QALY gained in patients with stage 1 ALS. At price reductions of more than 97%, the ICUR for edaravone remains more than $200,000 per QALY gained for patients treated in other stages.

The sensitivity analysis indicated that three factors can substantially lower the incremental cost-effectiveness of edaravone compared with standard of care: a substantial price reduction for edaravone, a higher level of effectiveness in the early stages of ALS, and hard-stopping rules after progression to stage 2 or 3 of the King's ALS clinical staging system.

Conclusions

CDR found that edaravone was not a cost-effective treatment for patients with ALS at any stage of the disease.

The ICUR of edaravone compared with standard of care ranges from $1,441,000 per QALY gained in patients with stage 1 ALS to $3,152,000 per QALY gained in patients with stage 3. A 95% price reduction is required to reduce the incremental cost-effectiveness ratio (ICER) to less than $200,000 per QALY gained in patients with stage 1 ALS, while even at a 97% price reduction, the ICUR remains more than $200,000 per QALY for patients treated in other stages.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted an economic model that captured health outcomes in quality-adjusted life-years (QALYs) for a cohort of ALS patients primarily in the early stages of the disease.[3] The model compares the current standard of care (interdisciplinary supportive care plus riluzole) with edaravone plus current standard of care. In the model, 85% of patients in both treatment arms received riluzole. The analytical time horizon was 20 years with quarterly (three-month) cycles for transitions. The analysis incorporated a discount rate of 1.5% per annum for costs and benefits. The analysis was conducted from the perspective of the Canadian publicly funded health care system; an analysis using a modified societal perspective was also presented.

The manufacturer assumed in the model that all patients, regardless of stage of disease, were eligible to receive edaravone. As well, it was assumed that some patients would discontinue edaravone treatment for unspecified reasons at rates that increased with disease severity. Patients who discontinued treatment continued receiving interdisciplinary supportive care (including riluzole).

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of ALS patients for each of the two comparators: standard of care and edaravone plus standard of care.

Health states in the model were defined based on the King's ALS clinical staging system with five health states:

- stage 1, functional involvement of one central nervous system (CNS) region
- stage 2, functional involvement of two CNS regions
- stage 3, functional involvement of three CNS regions
- stage 4a, functional involvement of between one and three CNS regions plus the need for gastrostomy
- stage 4b, functional involvement of between one and three CNS regions plus the need for non-invasive ventilation (tracheostomy).

In each cycle, individuals could die, their health could remain stable, or their disease could progress (Figure 1). The model structure permitted only forward disease progression (from stage 1 to stage 2; from stage 2 to stage 3; from stage 3 to stage 4A or 4B; and from stage 4A to stage 4B). Although the report states that "functional involvement of three anatomic regions is not a prerequisite for stage 4A or stage 4B," the model structure does not permit progression from stage 1 or stage 2 directly to stage 4A or 4B.

Patient Cohort

The base-case analysis focused on a mixed-severity cohort of patients representing the target population for reimbursement. Alternative patient cohorts, based on distribution of

ALS severity at clinical trial enrolment in various manufacturer-sponsored edaravone trials, were considered in the sensitivity analysis.

Model Inputs: Disease Natural History Parameters

For the purpose of the economic analysis, the manufacturer attempted to identify disease-progression rates and stage-specific mortality rates for the standard of care arm using the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.[5] The PRO-ACT database is a registry of patients who have participated in the placebo arms of phase ii and phase III trials. It includes data for more than 10,000 patients representing a geographically diverse set of patients in relatively diverse clinical settings (standard of care varies across countries). Patients in the database were assigned a King's ALS stage based on Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) assessments using a published algorithm (Figure 2).[6] The resulting transition matrix resulted in a median life expectancy of three to four years, which is longer than published estimates of average life expectancy. This finding is consistent with other reports in the literature. Specifically, also using the PRO-ACT database, Thakore et al.[7] found the estimated Markov model–transition probabilities substantially underestimated mortality and progression beyond 12 months of observation. Due to the inconsistency in the estimated life expectancy, the manufacturer's analysis did not use its analysis of the PRO-ACT database to directly inform disease-progression rates or mortality rates.

Ultimately, the progression rates for standard of care transition and mortality rates were estimated primarily via calibration. Six input parameters were estimated through calibration: the three-month progression probabilities for moving from stage 1 to stage 2, stage 2 to stage 3, stage 3 to stage 4A, stage 3 to stage 4B, and stage 4A to stage 4B, and the three-month probability of death for individuals with stage 1 disease. The mortality probabilities for individuals with ALS stage 2, 3, 4A, or 4B were calculated by multiplying the three-month probability of death for individuals with stage 1 disease by the relative rates of death for each stage compared with stage 1, as observed in the PRO-ACT database. The calibration targets were health-state residency times and overall life expectancy with ALS as reported by Balendra et al.,[8] who analyzed disease-progression rates in 725 ALS patients who participated in the Mito Target trial (UK population) and the LiCALS trial (European population).

The strengths of this approach are that it incorporates some of the information — such as the relative risk of mortality by stage of disease — from the PRO-ACT database, which represents a large and diverse population of ALS patients, and that it results in health-state residency times and overall life expectancy consistent with what was observed in two relatively large ALS trials.

Model Inputs: Treatment Effectiveness and Treatment Discontinuation

The manufacturer's submission indicates that they estimated a reduction in the decline in King's ALS clinical stage over six months by 25% based on the results of their pivotal study (Study 19).[9] The manufacturer then assumed that the three-month relative risk reduction was the same value, 25%, for all possible forward-progressing transitions. The manufacture's submission does not assume a direct effect of treatment on the transition to death.

Model Inputs: Treatment Adherence and Discontinuation

The manufacturer's analysis assumes that treatment discontinuation rates increase with increasing disease severity. The rates used are based exclusively on expert opinion.

Model Inputs: Costs

Cost of Treatment and Treatment Administration

The manufacturer's submission includes the costs of the drug, pre-treatment, the maintenance of a peripherally inserted central catheter (PICC), and drug administration.

The manufacturer's analysis assumes a daily cost of treatment of $1,424. Therefore, the drug cost is $19,943 in the first cycle
(14 days of treatment) and $14,245 in subsequent treatment cycles. The manufacturer's analysis assumes twelve 28-day treatment cycles per year.

Administration costs appear to be underestimated for patients who live in their own home or in a long-term care facility. For individuals who are living in their own home, the manufacturer's report indicates that patients will either travel to an administration clinic to receive edaravone infusions, or receive them at home through a home-care visit. Further, these patients (on their own or with the assistance of their caregivers) will be required to perform PICC maintenance three times each day. No costs are assumed for the administration of treatment to these patients [redacted]. In the base-case analysis, the full costs of these services (drug infusion and PICC maintenance supplies) should be included. A scenario analysis [redacted] with infusion centres across the country and home-care staff paid for by the manufacturer can be included as a separate analysis.

For individuals living in a nursing home, long-term care facility, or other health care facility, the manufacturer's report does not include personnel costs for treatment infusions or PICC maintenance. This was done to avoid double counting, as personnel costs are included in per diem charges. While per diem charges do include the costs of personnel in health care facilities, this does not accurately capture the opportunity cost of reassigning nurse care time to drug administration from other patient care responsibilities. The correct approach to account for the marginal cost of the personnel required is to estimate the time required to provide the additional services multiplied by the hourly rate for the level of skill required (i.e., 1.5 hours of nursing time multiplied by the average hourly wage of a nurse in Canada).

In the manufacturer's analysis, the proportion of patients who receive infusions in each setting was estimated based on expert opinion. The distribution assigned to patients in stage 1 does not add to 100% (it adds to 90%). Because the assumed administration costs are so low, this error does not impact the results.

Cost of All Other Publicly Funded Health Care

The manufacturer's analysis uses unit costs based on public payer sources for all other health care costs. The number of services used at each stage of disease was estimated using expert opinion and so is subject to substantial uncertainty. The total annual costs of each stage estimated by the manufacturer (Table 18) are substantially higher than the stage-specific or average health care costs of ALS reported in the literature (reviewed in the Gladman and Zinman[10] summary of recent literature in Table 19).

Costs Incurred by Patients, Their Families, and Other Societal-Perspective Costs of ALS

Out-of-pocket costs for assistive devices and copayments to health care facilities were included in the manufacturer's societal-perspective analysis. The manufacturer's analysis assumed annual indirect costs of $192 for stage 1; $2,580 for stage 2; $7,812 for stage 3; and $20,000 for stages 4A and 4B.

Model Inputs: Utilities

Health-state utilities were based on disease severity and derived from a study by Beusterien et al.[11] of societal-perspective (not patient-perspective) utilities. The values are relatively similar to another study, which reported patient quality-of-life estimates that were based on the EuroQol 5-Dimensions (EQ-5D) questionnaire.[12] For patients receiving treatment, no within-state disutility associated with treatment side effects or within-state utility improvement associated with non–stage altering symptom relief was incorporated into the manufacturer's analysis.

Model Validation

The manufacturer's economic report does not describe any model-validation exercises. Given there are few model-based analyses of ALS treatments, model-validation exercises would be useful. For example, it would be useful to validate the natural history progression estimates and assumptions against one of the many population cohort studies available. Similarly, simulating a patient population similar to the Trial 19 population would help demonstrate outcomes similar to those observed in the placebo arm of the trial.

Deterministic and Probabilistic Analysis

The manufacturer's base-case analysis, which assumed a mixed-severity cohort of patients, averaged the stage-specific incremental cost-effectiveness ratio (ICER) of edaravone compared with standard of care. A deterministic sensitivity analysis was performed on several parameters, typically considering a variation of ± 50% on the base case. However, this approach for administration costs did not capture the uncertainty in the base-case parameters, many of which were set to zero.

The manufacturer also included a probabilistic sensitivity analysis. The varied parameters included discontinuation rates, treatment effectiveness, drug cost, costs associated with drug administration, other health care costs, and utilities. All distributions were considered independent of each other and no rank ordering of effectiveness, costs, or utilities across states was implemented.

Manufacturer's Base Case

In the base case (deterministic), the manufacturer's analysis estimated that edaravone treatment increased average life expectancy (1.97 years versus 1.78 years), QALYs (0.97 QALYs versus 0.85 QALYs), and lifetime costs ($988,308 versus 765,832) compared with standard of care, resulting in an incremental cost-utility ratio (ICUR) of $1,957,200 per QALY gained (Table 22).

The probabilistic analysis identified the same average number of QALYs, very similar average costs ($992,215 versus 764,337), and an ICUR of $1,899,000 per QALY gained.

Summary of Manufacturer's Sensitivity Analyses

Deterministic sensitivity analyses were performed on the following:

- stage distribution of the population
- alternative source for stage-specific utilities
- alternative time horizons for analysis
- discount rate
- stage-specific health care costs
- some of the out-of-pocket costs to patients that were included (societal-perspective analysis).

These analyses reached the same general conclusion as the manufacturer's base-case analyses (ICUR > $1,500,000 per QALY gained) with respect to the cost-effectiveness of edaravone compared with standard of care.

Key insights from deterministic sensitivity analysis on influential model parameters included the following:

- Higher rates of treatment discontinuation decrease the ICUR of edaravone compared with standard of care.
- The ICUR for edaravone compared with standard of care may be as low as $1,500,000 per QALY gained if the treatment effect is a relative risk reduction of 0.3 (compared with the base case of 0.25).
- The ICUR for edaravone compared with standard of care is highly sensitive to the price of the drug. At a drug cost of $712 per administration (50% price reduction, compared with $1,424 in the base case), the ICUR falls to less than $1,000,000 per QALY gained. Using the model provided by the manufacturer, at a drug cost of $382 per administration (75% price reduction); the ICUR is $500,000 per QALY gained. At a drug cost of $132 per administration (~90% price reduction), the ICUR is $150,000 per QALY gained.
- In the limited societal-perspective analysis, which included a portion of the costs incurred by the patient and their family, the ICUR for edaravone decreased slightly from $1,957,200 per QALY gained to $1,955,500.

The manufacturer's probabilistic sensitivity analysis indicated there is a less than 3% probability that edaravone is cost-effective compared with standard of care at a willingness-to-pay threshold of $1,000,000 per QALY gained.

Limitations of Manufacturer's Submission

The following key limitations were noted in the manufacturer's analysis.

- **Model structure.** The model structure does not incorporate transitions from stage 1 to stage 3, stage 1 to stage 4A, stage 1 to stage 4B, stage 2 to stage 4A, or stage 2 to stage 4B. These transitions are important in order to accurately capture the natural history of ALS because functional involvement of all three regions is not a prerequisite for transition to stage 4A or 4B, as confirmed by the clinical experts consulted by CDR for this review.

  In order to calibrate the information obtained from the PRO-ACT database and to ensure a unique mathematical solution to the transition matrix, transitions from stage 1 to

stage 3 and from stage 1 or 2 to stage 4A or 4B were eliminated. This structural assumption violates one of the key observations of Balendra et al.[8] (italics added for emphasis):

"Of the total numbers of patients who reached stage 1, 2 or 3, more progressed to the consecutive stage at further assessment rather than skipping a stage or not moving from their stage by the end of the study period (Table 4). No patients moved to an earlier disease stage. For example, of all the 430 patients who reached stage 2 during the course of follow-up, none moved to stage 1, 54% were found to progress to the consecutive stage (stage 3) at further assessment, *17% were found to progress to stage 4 (and skipped stage 3) at further assessment*, 5.3% progressed to death (skipping stages 3 and 4) and 23.7% did not move from stage 3 during the rest of the follow-up period."

Balendra et al.[8] reported that 31.9% of stage 1 patients progress directly to stage 3, 4.6% of stage 1 patients progress directly to stage 4, and 17.0% of stage 2 patients progress directly to stage 4. Conditional on having progressed during the observation period of the trials, we calculate that 33.0% of stage 1 patients progress directly to stage 3, 4.8% of stage 1 patients progress directly to stage 4, and 22.3% of stage 2 patients progress directly to stage 4. Further review of the literature[7] confirms that permitting transitions from stage 1 to stage 3 and from stage 1 or 2 to stage 4A or 4B are important to accurately capture the natural history of the disease.

Table 2: Proportion of patients moving to each disease stage from the stage in the left column

	Total number of patients reaching this Stage during the course of follow-up	Proportion moving to Stage 1 (%)	Proportion moving to Stage 2 (%)	Proportion moving to Stage 3 (%)	Proportion moving to Stage 4 (%)	Proportion moving to Stage 5 (death) (%)	Proportion not moving from this Stage by the end of the study (%)
Stage 1	725	N/A	59.3	31.9	4.6	1.0	3.3
Stage 2	430	0	N/A	54.0	17.0	5.3	23.7
Stage 3	463	0	0	N/A	42.3	19.0	38.7
Stage 4	302	0	0	0	N/A	47.0	53.0

More patients at stages 1, 2 and 3 progressed to the consecutive disease stage than progressing to any other disease stage.
N/A, Not applicable.
The bold text refers to transition to the next consecutive stage.

Note: From the stage in the left column based on the observed disease-progression rates in 725 ALS patients who participated in the Mito Target trial (UK population) and the LiCALS trial (European population).

Source: Balendra et al..[6]

Notably, the challenges in fitting a single Markov-transition matrix to longer-term progression and mortality observations in the PRO-ACT database may require incorporating time-in-state detail. Thakore et al.[7] reported exploring this direction of analysis and found that semi-Markov models were computationally intractable, given the size of the PRO-ACT data set.

Comparing the standard of care transition matrix used in the manufacturer's analysis (Table 15, Table 16) with the matrices identified by Thakore et al.[7] using the PRO-ACT database (Table 16) reveals that the manufacturer's economic model assumes a higher mortality rate for later stages of disease (consistent with their specific effort to match overall mortality). This may be underestimating the progression out of stage 1 as well as the progression to later disease stages (stage 4A and 4B). Unfortunately, the prior cost-

effectiveness analyses[13,14] use different and less detailed health-state definitions that preceded the development of the King's ALS clinical staging system, so utilizing or comparing these analyses with the transition matrices from these studies would not be appropriate.

The CDR reanalysis used three-month health-state transitions based on the analysis of Thakore et al.[7] to ensure the inclusion of transitions from stage 1 to stages 3, 4A, and 4B as well as transitions from stage 2 to 4A and 4B. The transition matrix presented in the study by Thakore et al.[7] was modified to exclude backward transitions (Table 3).

Table 3: ALS Health-State Transition Matrices (Three-Month Transition Probabilities) for Patients Receiving Standard of Care, Based on the PRO-ACT Database Analysis

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.537	0.307	0.094	0.025	0.032	0.005
Stage 2		0.586	0.302	0.027	0.067	0.018
Stage 3			0.773	0.054	0.121	0.052
Stage 4A				0.838	0.121	0.041
Stage 4B					0.861	0.139

ALS = amyotrophic lateral sclerosis; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials Database.

Source: Thakore et al.[7] modified to exclude backward transitions.

- **Patient heterogeneity.** Important characteristics of the initial cohort — including patient age, gender, and site of onset or progression rate prior to diagnosis — were not described or varied in the scenario analyses. The sensitivity analysis did not explore the heterogeneity in the disease-progression rates associated with these patient characteristics.

  Specifically, patient age, site of onset, and time in state are considered important predictors of disease-progression rates. For example, using the PRO-ACT database, Atassi and colleauges[5] reported that older age at symptom onset was a significant predictor of shorter overall survival (hazard ratio [HR] 2.25, $P < 0.001$) and Thakore et al.[7] reported that increasing age had a significant impact on stage-specific mortality (HR 1.4 to 1.6). Atassi and colleauges[5] reported that bulbar onset is a significant predictor of shorter overall survival (HR 1.24, $P = 0.04$), and Thakore et al.[7] reported that bulbar onset increases stage-specific progression rates overall and, specifically, the transitions from stages 1 and 2 to stage 4A. These specific findings confirm earlier reports on smaller cohorts and recent reports on international cohorts.[15-18]

  Given that the substantial heterogeneity in patient progression is at least associated with characteristics such as age of onset, gender, and site of onset, stratifying the analysis by some of these features may provide important additional insights.[5,7,15-18]

- **Initial cohort ALS severity distribution.** The cost-utility analysis was performed for a cohort of patients with a distribution of disease severities. Ideally, the cost-effectiveness analysis would be performed separately for groups of patients who were distinguishable on personal or clinical characteristics at the time the treatment decision was made (including disease severity, but also other features that may affect the rate of disease progression such as age, gender, site of onset, and progression rate prior to diagnosis, as discussed previously). Performing the analysis on a mixed cohort of patients with different ALS clinical stages averaged the stage-specific ICUR of edaravone compared

with placebo, which may be masking a lower ICUR in some clinical stages and a higher ICUR in others.

- The initial cohort patient-severity distribution was calculated using the median time spent in each health state. Specifically, with an adjusted median stage 1 length of 12 months, the proportion of the ALS patient population in each ALS state was estimated using the median time in the state divided by the sum of the median durations. Using stage 2 as an example, 5.5 months ÷ (12.0 + 5.5 + 6.7 + 5.9 + 3.2) = 17.0% (Table 4). This mathematical approach would not accurately result in the cross-sectional distribution of current ALS patient's health stages.

Table 4: Initial Patient Cohort ALS Severity Distribution

	Distribution of Patients by ALS Health State (Using King's Clinical Stage)				
	Stage 1	**Stage 2**	**Stage 3**	**Stage 4A**	**Stage 4B**
Median months spent in each health state[8] (95% CI)	18.1[a] (17.4 to 18.5)	5.5 (4.1 to 5.9)	6.7 (6.0 to 8.1)	5.9 (4.6 to 7.6)	3.2 (2.5 to 4.1)
Base-case patient cohort	36.0%	17.0%	20.0%	18.0%	9.0%

ALS = amyotrophic lateral sclerosis; CI = confidence interval.

[a] Balendra et al.[8] reported the median time in each disease stage based on 725 patients in two clinical trials. They stated that they believe 18 months might be an artificially long estimate due to recall bias, so the authors of the economic analysis adjusted this time to 12 months.

- **Effect of edaravone.** Treatment effect was estimated using a relative risk reduction. In general, relative risk reductions are not constant over different time durations, they change as the proportions of the population in each group are declining. Because relative risk reductions are not constant over different observation durations, treatment effects on transition rates would ideally be applied using rate ratios and then the resulting transition probabilities calculated. Given the short life expectancy of patients with ALS, this assumption is unlikely to cause a significant impact on this economic evaluation. Further, treatment effect was assumed to be constant across ALS clinical stages, which is inconsistent with the following: the physiological mechanism of delayed progression through the inhibition of motor neuron death, with the results stratified by Japanese ALS severity level in Trial 19,[19] and the evidence provided by Study 18.[20]

  The manufacturer's submission relies on Trial 19,[19] a study that focused on a population of patients in the early stages of ALS (39.4% in stage 1; 46.0% in stage 2; and in 14.6% stage 3), to estimate treatment effect. This study found a statistically significant change in their primary end point, the least squares–adjusted change in ALSFRS-R. The regression analysis included three dynamic allocation factors, including whether the patient was younger than age 65, diagnostic criteria (definite versus probable), and change about the observation period. However, this analysis did not use the King's ALS clinical staging system and so the effect size is not directly applicable to the model used in the economic analysis.

  To estimate the relative risk reduction in the decline in King's ALS clinical stage for the model-based analysis, the manufacturer categorized the clinical trial (Trial 19) patients into King's ALS clinical stages based on their ALSFRS-R assessments using a published algorithm.[6] Because 80% of the patients who dropped out of the trial had experienced a decline in King's ALS clinical stage, the manufacturer used the time to first progression to estimate treatment effect. Progression-free survival rates using King's ALS clinical stage to define progression are not presented in the published trial results but are provided in Figure 2 of the economic report. Specifically, the manufacturer reported a six-month

progression-free survival rate of 55.9% in the edaravone arm and 42% in the placebo arm (relative risk reduction [RRR] = 25%).

The manufacturer's submission does not use the clinical trial data to estimate stage-specific relative risk reductions. However, information available in the appendix of Trial 19 presents the shift in the Japanese ALS severity classification stratified by severity at the start of the trial.[19] This crude information implies that patients with Japanese ALS stage 1 (able to work or perform housework) treated with edaravone may experience a progression delay. However, this information does not provide evidence of a progression delay in patients with Japanese ALS stage 2 (independent living but unable to work). This is consistent with the findings of Study 18, which focused on patients with more severe disease (Japanese ALS severity level 3, requiring assistance for eating, excretion, or ambulation).[20] This small-sample exploratory study indicated no difference in the change in ALSFRS-R score over 24 weeks between the two treatment groups (*P* value = 0.835).

The combined clinical trial evidence suggests that treatment efficacy may vary by stage of disease, with greater effectiveness in patients with early-stage disease[19] and no or lesser effectiveness in patients with later-stage disease.[19,20] This is consistent with the physiological mechanism of delayed progression through the inhibition of motor-neuron death.

In summary, the magnitude of the treatment effect estimated in the manufacturer's analysis may slightly underestimate the overall treatment effect. This is specifically true for the treatment effect in patients with early-stage ALS, as the evidence submitted does not warrant the strong assumption that the same reduction in disease progression for patients with early-stage disease should be assumed for those with later-stage disease. Treatment effect for patients with later-stage ALS may therefore be overestimated.

Using the event-free survival graph provided by the manufacturer in the economic report, CDR estimated the annual rate of disease progression assuming a constant hazard. Specifically, since 42.0% of patients receiving edaravone experienced disease progression by six months, we estimate the annual rate of disease progression to be 1,089 per 1,000 patient-years
(= −ln [1−0.420] ÷ 0.5 years × 1,000). Similarly, since 55.9% of patients receiving placebo experienced disease progression by six months, we estimate the annual rate of disease progression to be 1,637 per 1,000 patient-years [= −ln (1−0.559) ÷ 0.5 years × 1,000]. We then calculate the HR to be 0.665 (95% confidence interval [CI], 0.41 to 1.08).

To apply the effectiveness to the natural history, the three-month transition probabilities were converted to annual rates, the HRs for treatment were applied to all forward-transition rates, and then the new transition rates were converted back to three-month transition probabilities. The three-month ALS health-state transitions for patients receiving standard of care plus edaravone are presented in Table 5.

Table 5: ALS Health-State Transition Matrices (Three-Month Transition Probabilities) for Patients Receiving Edaravone Plus Standard of Care (CDR Reanalysis)

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.677	0.217	0.064	0.017	0.021	0.005
Stage 2		0.706	0.213	0.018	0.045	0.018
Stage 3			0.830	0.036	0.082	0.052
Stage 4A				0.877	0.082	0.041
Stage 4B					0.861	0.139

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review.

- **Issues with the total treatment cost.** The model uses a three-month cycle length and, in each cycle, provides three 28-day cycles of treatment. Over the course of a year, this results in 12 treatment cycles and a total annual cost of $170,938. However, there are thirteen 28-day cycles in a year, resulting in an actual total annual cost of $185,182 and an underestimation in treatment costs of $14,245. In order to spread the cost of one additional treatment cycle evenly over the year, CDR reanalysis assumed a daily treatment cost of $1,543 and adjusted the induction-month costs to ensure the total treatment costs for the first year were $190,880 (equivalent to 134 treatment days at $1,424.48 per day).
- **Issues with the estimates of health-state costs.** The non-drug ALS stage–specific health care costs in the manufacturer's analysis are substantially greater than the costs reported in the literature (Table 18).

  There is only one study reporting the direct medical costs associated with ALS care in Canada.[21] This study reported the publicly funded direct medical costs for ALS patients with home mechanical ventilation to be $5,042 per month ($60,504 per year in 2015 Canadian dollars). There are no studies of the direct medical costs associated with other stages of ALS care in Canada. In other countries, where stage-specific direct health care costs are available, costs increase with disease severity.[22-24]

  While there is substantial variation in the reported costs of medical care for patients with ALS, adjusting for currency and inflation, average annual costs are similar across health systems where standard of care is comparable (Table 19). Specifically, average annual costs range from $25,811 to $36,621 (in 2017 Canadian dollars) when focusing on reports from Denmark,[25] Germany,[24] Ireland,[26] the Netherlands,[22] and the US.[27] Importantly, severity-stratified costs are available for Germany and the Netherlands.

  Based on the severity-stratified costs available for Germany and the Netherlands, as well as the direct medical costs for ALS patients with home mechanical ventilation in Canada,[21] the CDR reanalysis used the stage-specific annual health care costs presented in Table 6.

Table 6: King's ALS Clinical Stage–Specific Direct Health Care Costs (CDR Reanalysis)

King's ALS Clinical Stage	CDR Base Case ($)	Range ($)	Justification
Stage 1	8,805	5,000 to 13,125	• Estimated direct medical costs for German cohort requiring no assistance with ADL[24]
Stage 2	26,500	10,000 to 33,100	• Estimated direct medical costs for Dutch cohort with ALSFRS items 30–40[22]
Stage 3	36,800	17,900 to 90,000	• Estimated direct medical costs for German cohort requiring assistance with ADLs[24] • Consistent with estimated direct medical costs for Dutch cohort with ALSFRS items 20–30[22]
Stage 4A	47,900	33,100 to 116,000	• Estimated direct medical costs for German cohort requiring artificial nutrition[24] • Consistent with estimated direct medical costs for Dutch cohort with ALSFRS items 0–20[22]
Stage 4B	60,500	50,000 to 150,000	• Estimated direct medical costs for ALS patients with home mechanical ventilation in Canada[21] • Consistent with estimated direct medical costs for German cohort requiring artificial ventilation[24]

ADL = activities of daily living; ALS = amyotrophic lateral sclerosis; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; CDR = CADTH Common Drug Review.

- Estimates of administration costs. Drug administration costs for patients receiving infusions at home or who could travel to an infusion clinic were assumed to be covered [redacted]. [redacted] the public payer will be responsible for providing these services and there is no clear mechanism to ensure the provision or long-term maintenance of such a program. Reduced drug administration costs [redacted] should be considered in a scenario analysis only. Drug administration costs for patients living in a health care facility were also assumed to be zero from a public payer perspective because personnel costs are included in per diem charges. This does not appropriately account for the marginal consumption of nursing resources.
- To fully account for the opportunity cost of the nurse time required to administer treatment to patients in a nursing, long-term care, or hospital facility, the CDR reanalysis incorporated an administration cost of $64.73. This rate assumes 90 minutes of nursing care (60 minutes of treatment time and 15 minutes on either side of the administration to prepare both the medication and the patient and then to wrap up and clean up) at an average hourly rate of $43.15 ($38.19 per hour plus 13% to account for benefits).[28]
- To fully account for the cost of administration to treat patients living at home, the CDR reanalysis assumed that a two-hour home-care visit from a nurse would be required at a cost of $130. The estimated cost of home care was based on the hourly rates for representative private care ($65 per hour[29]).
- Estimates of societal-perspective costs. Out-of-pocket costs for assistive devices and copayments to health care facilities were included in the manufacturer's societal-perspective analysis. However, patients appear to incur significantly higher out-of-pocket costs (private home care, travel to and from frequent medical appointments, home renovations, durable medical equipment, etc.) and indirect costs through lost wages and unpaid caregiving time than were included in the manufacturer's analysis. The manufacturer's analysis assumed annual indirect costs of $192 for stage 1; $2,580 for stage 2; $7,812 for stage 3; and $20,000 for stages 4A and 4B. In contrast, one

Canadian study estimated that patients themselves incur approximately $32,337 in annual costs (2014 Canadian dollars), of which approximately one-third is reimbursed through government non-health programs (specifically, not publicly funded health insurance) or charity support.[30]

To more fully account for the out-of-pocket costs paid for by patients and their families and those paid through charitable donations or government programs separate from the public health care payer, the CDR reanalysis used the annual out-of-pocket costs for patients and their families by disease stage, scaled up by 65% to include costs supported by government non-health programs and non-profit organizations, and adjusted for inflation. In comparison with the manufacturer's analysis, the CDR reanalysis assumes societal-perspective costs are much higher for earlier stages of ALS and more similar across disease stages. This is consistent with investments in renovations (to accommodate both actual and expected future health changes) as well as the costs for the significant levels of assistance patients require before they gain access to the intensive personal-support care available through public health insurance during the later stages of ALS.

Table 7: Stage-Specific Societal-Perspective Costs of Care for Patients With ALS (CDR Reanalysis)

	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B
Annual costs ($)	20,040	20,040	45,500	38,200	38,200

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review.

Note: Costs presented in 2017 Canadian dollars. Costs include out-of-pocket costs incurred by families or paid for by government non-health programs and non-profit organizations.

Source: Gladman et al..[30]

CADTH Common Drug Review Reanalyses

As noted in the limitations section, CDR identified several important shortcomings relating to the manufacturer's model. CDR presents a revised analysis stratified by stage of disease. Results are not presented for patients in stage 4B because there is no treatment benefit at this stage (in either the manufacturer's or CDR's analysis).

The modifications to the manufacturer's model included:

- changes to the ALS natural history transitions so as to enable progressive transitions to non-adjacent health states
- using a constant hazard rate and hazard rate–ratio approach for estimating effectiveness
- revised treatment costs to include 13 treatment cycles per year
- revised costs for drug administration
- revised costs for non-drug ALS stage–stratified health care.

In addition, because only 90% of stage 1 patients were assigned an administration setting in the manufacturer's analysis, the CDR reanalysis assumed the proportion receiving edaravone at home to be 50% (ensuring that 100% of patients were assigned an administration setting).

Key Sensitivity Analysis

CDR reanalysis also included the following exploratory scenario and sensitivity analyses.

Sensitivity analyses were conducted on:

- mortality rates, including one analysis with mortality rates consistent with the manufacturer's analysis
- the natural history of disease-progression rates (specifically, varying disease-progression rates using HRs of 0.5, 0.75, 1.25, 1.5, and 2.0 in order to explore how patient-specific factors that influence disease progression may affect the cost-effectiveness of edaravone compared with standard of care)
- treatment discontinuation rates and treatment-stopping rules for access to treatment after disease progression
- the annual cost of stage-specific non-drug health care
- the annual cost of treatment
- the societal-perspective costs incurred by patients and families.

In addition, exploratory scenario analyses were conducted on which treatment has a differential effectiveness by stage of disease.

Results of CDR Reanalysis: Base Case

The CDR base-case analysis (deterministic) stratified by the patient's initial King's ALS clinical stage is presented in Table 8. This analysis identified that treatment provides a greater gain in life expectancy and quality-adjusted life expectancy among patients with earlier-stage disease. As a result, the ICUR of edaravone compared with the current standard of care is the lowest for patients in stage 1 ($1,441,000 per QALY gained) and greatest for patients in stage 3 ($3,152,000 per QALY gained).

Results were provided deterministically in the CDR reanalyses, as there was not much variation between probabilistic and deterministic results, but life-years were reported only when the model was run deterministically.

Table 8: Results of Reanalysis Using CDR Base Case

	Edaravone Plus Standard of Care	Standard of Care	Incremental
King's ALS Clinical Stage 1			
Costs	$534,517	$149,767	$384,750
Life-years	3.565	3.180	0.385
QALYs	1.606	1.339	0.267
Incremental cost-effectiveness ratio			
Cost per life-year gained			$999,093
Cost per QALY gained			**$1,440,786**
King's ALS Clinical Stage 2			
Costs	$462,880	$146,672	$316,208
Life-years	3.124	2.859	0.265
QALYs	1.250	1.086	0.163
Incremental cost-effectiveness ratio			
Cost per life-year gained			$1,194,456
Cost per QALY gained			**$1,937,004**

	Edaravone Plus Standard of Care	Standard of Care	Incremental
King's ALS Clinical Stage 3			
Costs	$400,156	$137,527	$262,630
Life-years	2.692	2.534	0.158
QALYs	0.953	0.869	0.083
Incremental cost-effectiveness ratio			
Cost per life-year gained			$1,662,320
Cost per QALY gained			**$3,152,352**
King's ALS Clinical Stage 4A			
Costs	$372,434	$155,935	$216,499
Life-years	2.824	2.667	0.156
QALYs	0.993	0.916	0.078
Incremental cost-effectiveness ratio			
Cost per life-year gained			$1,385,057
Cost per QALY gained			**$2,785,312**

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

Costs reported in 2017 Canadian $.

Results of CDR Reanalysis: Sensitivity Analysis

The CDR reanalysis explored several issues using deterministic sensitivity analysis. The results of these analyses are presented in Table 9. A summary of key observations is presented here.

Mortality: Assumptions around the base-case mortality rate did not have a meaningful impact on the ICER. This is likely due to the fact that treatment does not directly impact the mortality rate.

Disease progression: For patients with early-stage disease, the ICER of edaravone is lower in patients with more slowly progressing disease and greater in patients with more rapidly progressing disease. In contrast, in patients with later-stage disease, the ICER of edaravone is greater in patients with more slowly progressing disease and lower in patients with more rapidly progressing disease.

Treatment effectiveness: The cost-effectiveness of edaravone is highly influenced by the effectiveness of the drug to slow disease progression. If disease progression can be slowed dramatically (HR = 0.41, compared with the base-case estimate of 0.665), then the treatment of patients in stage 1 and 2 has an ICER of less than $1,000,000 per QALY gained. However, there is substantial uncertainty about the effectiveness of treatment. If treatment reduces the progression rate by only 20% (HR = 0.8), then the ICER of edaravone exceeds $2,500,000 per QALY gained for patients at all stages of disease.

Treatment effectiveness by stage of disease: Edaravone may be more effective in slowing progression in patients with earlier-stage disease than those with later-stage disease. If that is the case, the ICER of edaravone decreases for earlier stages of disease and increases for later stages. If nearly all treatment effectiveness is attributed to reduced disease progression in patients with stage 1 disease (HR in stage 1 = 0.3), then the ICER of edaravone for treating patients in stage 1 is $716,000 per QALY gained.

Treatment discontinuation: The cost-effectiveness of edaravone is highly sensitive to treatment-stopping policies. If no treatment-stopping policies are in place and patients choose to continue treatment indefinitely, edaravone becomes substantially less cost-

effective than in the base case. For example, in patients with stage 1 ALS, the ICER increases from $1,441,000 per QALY gained to $2,150,000 per QALY gained.

Treatment-stopping policies: Strict treatment-stopping policies after a specific threshold level of disease progression improves the cost-effectiveness of edaravone. For example, terminating treatment after progression to stage 3 improves the ICER of edaravone for treating patients with stage 1 disease from $1,441,000 per QALY gained to $1,131,000 per QALY gained and improves the ICER of edaravone for treating patients with stage 2 disease from $1,937,000 per QALY gained to $1,414,000 per QALY gained.

Non-drug stage-specific direct health care costs: The stage-specific costs of other health care did not substantively influence the cost-effectiveness of edaravone compared with standard of care.

Societal-perspective costs incurred by patients and families: Incorporating higher societal-perspective costs for early stages of disease (stage 1 through 3) did not substantively influence the cost-effectiveness of edaravone compared with standard of care.

Table 9: Key Sensitivity Analysis Compared With the CDR Base Case

	ICUR ($ per QALY Gained) for Edaravone Plus Standard of Care Versus Standard of Care			
	Stage 1	Stage 2	Stage 3	Stage 4A
Base Case	**1,441,000**	**1,937,000**	**3,152,000**	**2,786,000**
Mortality rate				
Lower than CADTH base case (25% reduction)	1,437,000	1,901,000	2,960,000	2,654,000
Higher than CADTH base case (25% higher)	1,443,000	1,970,000	3,348,000	2,919,000
Manufacturer's base case	1,407,000	1,949,000	3,562,000	4,703,000
Disease-progression rate (no treatment)				
Slow progressing (HR = 0.5)	1,280,000	1,839,000	3,794,000	3,173,000
Moderate–slow progressing (HR = 0.75)	1,364,000	1,882,000	3,333,000	2,885,000
Moderate–fast progressing (HR = 1.25)	1,513,000	1,998,000	3,083,000	2,761,000
Rapid progressing (HR = 1.5)	1,582,000	2,062,000	3,068,000	2,775,000
Very rapid progressing (HR = 2.0)	1,713,000	2,197,000	3,121,000	2,861,000
Treatment effectiveness: All stages				
More effective on all stages (HR = 0.41)	725,000	991,000	1,702,000	1,518,000
Less effective on all stages (HR = 0.80)	2,535,000	3,386,000	5,408,000	4,756,000
Very low effectiveness (HR = 0.95)	10,648,000	14,147,000	22,227,000	19,452,000
Differential effect by stage of disease[a]				
HR1 = 0.30; HR2 = 0.90; HR3 = 0.90; HR4A = 0.90	716,000	6,976,000	11,014,000	9,655,000
HR1 = 0.40; HR2 = 0.80; HR3 = 0.95; HR4A = 0.95	915,000	4,466,000	22,227,000	19,452,000
HR1 = 0.50; HR2 = 0.75; HR3 = 0.84; HR4A = 0.84	1,122,000	3,013,000	6,810,000	5,981,000
HR1 = 0.50; HR2 = 0.70; HR3 = 1.0; HR4A = 1.0	1,140,000	3,077,000	NA	NA
HR1 = 0.60; HR2 = 0.60; HR3 = 1.0; HR4A = 1.0	1,347,000	2,133,000	NA	NA
Treatment stopping				
No treatment quitting (everyone continues)	2,150,000	2,855,000	4,310,000	3,914,000
No treatment ≥ stage 4B	1,617,000	2,056,000	2,940,000	2,684,000
No treatment ≥ stage 4A	1,499,000	1,948,000	2,971,000	NA
No treatment ≥ stage 3	1,131,000	1,414,000	NA	NA
No treatment ≥ stage 2	961,000	NA	NA	NA

	ICUR ($ per QALY Gained) for Edaravone Plus Standard of Care Versus Standard of Care			
	Stage 1	Stage 2	Stage 3	Stage 4A
Non-treatment health care costs				
All lowest values	1,424,000	1,905,000	3,106,000	2,752,000
All higher values	1,446,000	1,944,000	3,209,000	2,903,000
Societal perspective				
CDR values	1,476,133	1,981,921	3,247,419	2,862,131

CDR = CADTH Common Drug Review; HR = hazard ratio; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Scenarios were established to result in approximately the same weighted average effectiveness as observed in the Study 19 trial.

Results of CDR Reanalysis: Price Reduction

The cost-effectiveness of edaravone is highly sensitive to the cost of the drug treatment. In the manufacturer's analysis, the base-case cost was $1,424 per day. At a treatment cost of less than $400 per day, the ICER for stage 1 patients falls below $500,000 per QALY gained, and at a treatment cost of less than $250 per day, the ICER for stage 2 patients falls below $500,000 per QALY gained. At the lowest considered treatment cost of $14 per day (99% price reduction), the ICER of treating stage 1 patients is $148,000 per QALY gained and the ICER of treating stage 2 patients is $205,000 per QALY gained.

Table 10: Price Reduction for Edaravone for CDR Base Case

Percentage of Base Case	Daily Cost of Edaravone ($)	Annual Cost ($) (130 Treatment Days per Year)	Incremental Cost-Effectiveness Ratio ($ per QALY Gained)				
			Manufacturer's Base Case (120 Treatment Days per Year)	Stage 1	Stage 2	Stage 3	Stage 4A
115%	1,638	212,960	2,256,000	1,637,000	2,200,000	3,582,000	3,159,000
Base case	**1,424**	**185,182**	**1,957,000**	**1,441,000**	**1,937,000**	**3,152,000**	**2,785,000**
92.3%	1,314	170,880[a]	1,803,000	1,340,000	1,802,000	2,932,000	2,593,000
90%	1,282	166,664	1,758,000	1,310,000	1,762,000	2,866,000	2,536,000
80%	1,140	148,146	1,559,000	1,180,000	1,587,000	2,580,000	2,287,000
70%	997	129,628	1,360,000	1,049,000	1,412,000	2,294,000	2,038,000
60%	855	111,109	1,161,000	919,000	1,237,000	2,007,000	1,789,000
50%	712	92,591	962,000	788,000	1,062,000	1,721,000	1,540,000
40%	570	74,073	762,000	657,000	887,000	1,434,000	1,291,000
30%	427	55,555	563,000	527,000	712,000	1,148,000	1,042,000
25%	356	46,296	464,000	461,000	625,000	1,005,000	917,000
20%	285	37,036	364,000	396,000	537,000	862,000	793,000
15%	214	27,777	265,000	331,000	450,000	718,000	668,000
10%	142	18,518	165,000	265,000	362,000	575,000	543,000
5%	71	9,259	65,000	200,000	275,000	432,000	419,000
2.5%	36	4,630	16,000	168,000	231,000	360,000	357,000
1%	14	1,852	Cost saving	148,000	205,000	317,000	319,000

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

[a] This amount ($170,880) is the annual treatment cost for twelve 10-day cycles at a daily price of $1,424.

Issues for Consideration

The manufacturer did not explicitly consider the cost of treating adverse events in the model. Among patients with greater experience with edaravone, serious adverse events may emerge, which could increase the costs associated with treatment with edaravone and, as such, further increase the ICUR. Bruising or contusions, gait disturbance, headache, dermatitis, and eczema were the most common adverse reactions observed in 10% or more of edaravone-treated patients. The most serious adverse effects reported across the clinical trials and in the post-marketing data analysis were hypersensitivity and sulphite allergic reactions, including anaphylactic symptoms (as per the CDR Clinical Report).

Patient Input

The ALS Society of Canada (ALS Canada), in coordination with seven provincial ALS societies, provided input for the edaravone review. ALS Canada collected information regarding the disease that was used to inform this patient input summary through a survey and three focus groups.

ALS Canada noted there are a variety of symptoms associated with ALS, and they worsen as the patient becomes increasingly paralyzed. The deterioration of motor neurons and the inability to control the muscles of the body lead to muscular atrophy. This imposes a significant challenge on many tasks that are performed on a daily basis. The muscular atrophy causes muscle fatigue and discomfort, cramps and twitches, as well as muscle stiffness and rigidity. Despite exhaustion, patients have trouble sleeping. There are also reports of symptoms such as headaches, stomach problems, itchiness, and both muscle and nerve pain. Assistance is often required for everyday tasks such as walking, transitions from sitting to standing, and transitions from lying to sitting. The need for assistance is quite demanding for caregivers, who also report having to plan their day around being able to provide that support. ALS may also lead to issues with breathing as a result of cramping or weakness of the diaphragm. In more severe cases, a feeding tube may be required, which also affects caregivers and families. The progression of disease also makes communication difficult for patients. As a result of the various, debilitating ways ALS affects one's life, the disease has a significant impact on the mental health of some patients.

Edaravone is administered intravenously at home, in hospital, or at a combination of hospital/outpatient clinic and home. While this overcomes the issue associated with swallowing pills, patients and caregivers expressed that accessing the appropriate services to receive the infusions was difficult, inconvenient, costly, and time-consuming. Some patients reported using a PICC line or Port-a-Cath, which requires regular daily maintenance and was noted as limiting for caregivers, as it "interferes with daily life."

The manufacturer considered the involvement of CNS regions, need for gastrostomy, and use of non-invasive ventilation as part of the defined model health states. The manufacturer conducted the analysis from the perspective of the public health care payer, but also considered a broader (societal) perspective considering indirect costs, such as: assistive devices, nursing home costs, and continuing/transition care. This did not capture considerations for the caregiver.

Conclusions

CDR found that, when compared with current standard of care, edaravone treatment increases life expectancy by two to five months and increases quality-adjusted life expectancy by one to three months. However, edaravone treatment increases lifetime health care costs by $200,000 to $385,000 per patient. As a result, the ICUR of edaravone compared with standard of care ranges from $1,441,000 per QALY gained in patients with stage 1 ALS to $3,152,000 per QALY gained in patients with stage 3 ALS. A 95% price reduction is required to reduce the ICUR to less than $200,000 per QALY gained in patients with stage 1 ALS. At price reductions of more than 97%, the ICUR for edaravone remains more than $200,000 per QALY gained for patients treated in other stages.

The sensitivity analysis indicated that three factors can substantially lower the incremental cost-effectiveness of edaravone compared with standard of care: a substantial price reduction, a higher level of effectiveness in the early stages of ALS, and hard-stopping rules after progression to King's ALS clinical stage 2 or 3.

Appendix 1: Cost Comparison

The comparators presented in Table 11 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 11: CDR Cost Comparison Table for Drugs Indicated for the Treatment of ALS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Edaravone (Radicava)	30 mg/ 100 mL	Solution for IV infusion	1,424.4800[a] per two 30 mg bags	60 mg infusion over one hour daily for 14 days followed by 14 days off. Subsequent cycles consist of a 60 mg infusion daily on 10 of 14 days followed by 14 days off.	Initial 28-day cycle: 712.24 Subsequent 28-day cycles: 508.74	Initial year: 190,880[c] Subsequent years: 185,182[b]
Riluzole (generics)	50 mg	Tablet	7.3630[c]	50 mg every 12 hours	14.73	5,360[c]

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review; IV = intravenous.

[a] Manufacturer-submitted price.

[b] Annual drug cost assumes 364 days, equivalent to thirteen 28-day cycles.

[c] Ontario Drug Benefit Formulary list price (August 2018).[31]

Appendix 2: Summary of Key Outcomes

The following summaries have been provided based on the CADTH Common Drug Review base case.

Table 12: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Edaravone Versus Standard of Care?

Edaravone Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	CDR base case: • stage 1: $1,441,000 per QALY • stage 2: $1,937,000 per QALY • stage 3: $3,153,000 per QALY • stage 4a: $2,786,000 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 13: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”			
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	Description of how the manufacturer established the natural history transition matrix was somewhat unclear (there was a detailed description of an approach they ultimately decided not to use and a brief description of the approach they did use). The report presents a different matrix for the treatment arm than the model (the matrix presented in the model was consistent with the description of the methods in the report).		

Table 14: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

CADTH

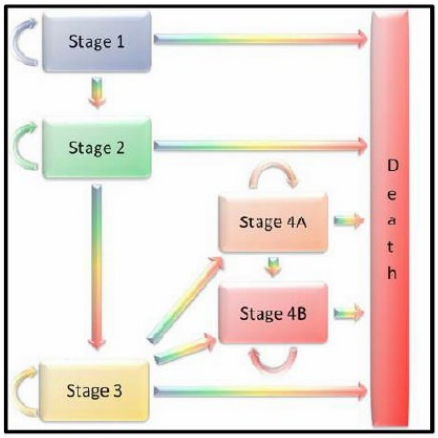
Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Edaravone has not been reviewed by the National Institute for Health and Care Excellence (NICE; UK), the Scottish Medicines Consortium (SMC; Scotland), or the Pharmaceutical Benefits Advisory Committee (PBAC; Australia) for the requested CADTH Common Drug Review indication.

Appendix 5: Reviewer Worksheets

Model Structure

Figure 1: Model Health States and ALSFRS-R Item Mapping



ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised.

Source: Manufacturer's economic submission.[3]

Figure 2: Model Health States and ALSFRS-R Item Mapping

King's Stage	Definition	Item Mapping
1	Functional involvement of one CNS region	Bulbar involvement -- Score ≤3 on Q1, Q2, or Q3
2	Functional involvement of two CNS regions	Upper limb involvement -- Score ≤3 on Q4 or Q5A
3	Functional involvement of three CNS regions	Lower limb involvement -- Score ≤3 on Q8
4A	Need for gastrostomy	If Q5B is answered, rather than Q5A
4B	Need for non-invasive ventilation	Score of 0 on Q10 *or* score ≤3 on Q12
5	Death	

CNS = central nervous system; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised.

Note: CNS regions are bulbar, upper limb, and lower limb.

Source: Manufacturer's economic submission.[3]

Table 15: Proportion of Patients Moving to Each Disease Stage (Balendra et Al.)

	Total number of patients reaching this Stage during the course of follow-up	Proportion moving to Stage 1 (%)	Proportion moving to Stage 2 (%)	Proportion moving to Stage 3 (%)	Proportion moving to Stage 4 (%)	Proportion moving to Stage 5 (death) (%)	Proportion not moving from this Stage by the end of the study (%)
Stage 1	725	N/A	59.3	31.9	4.6	1.0	3.3
Stage 2	430	0	N/A	54.0	17.0	5.3	23.7
Stage 3	463	0	0	N/A	42.3	19.0	38.7
Stage 4	302	0	0	0	N/A	47.0	53.0

More patients at stages 1, 2 and 3 progressed to the consecutive disease stage than progressing to any other disease stage.
N/A, Not applicable.
The bold text refers to transition to the next consecutive stage.

Note: From the stage in the left column based on the observed disease-progression rates in the 725 ALS patients who participated in the Mito Target trial (UK population) and the LiCALS trial (European population).

Source: Balendra et al..[8]

Table 16: ALS Health-State Transition Matrix (Three-Month Transition Probabilities) for the Standard of Care Arm Used in the Manufacturer's Analysis

From/ To	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.75	0.24				0.01
Stage 2		0.49	0.47			0.03
Stage 3			0.60	0.15	0.15	0.10
Stage 4A				0.83	0.01	0.15
Stage 4B					0.64	0.36

ALS = amyotrophic lateral sclerosis.

Note: Empty cells represent zero probability of transition.

Source: Manufacturer's economic report, Table 5.[3]

Table 17: ALS Health-State Transition Matrices (All Presenting Three-Month Transition Probabilities) for Patients Receiving Standard of Care (Thakore et al.)

Allowing Backward Transitions

Based on three-month transition matrix

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.53	0.31	0.09	0.03	0.03	0.01
Stage 2	0.10	0.49	0.30	0.03	0.07	0.02
Stage 3	0.01	0.12	0.64	0.05	0.12	0.05
Stage 4A			0.04	0.79	0.12	0.04
Stage 4B			0.04	0.03	0.78	0.14

Based on six-month transition matrix[b]

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.64	0.18	0.11	0.02	0.04	0.01
Stage 2	0.05	0.63	0.20	0.03	0.07	0.03
Stage 3	0.01	0.07	0.72	0.04	0.10	0.06
Stage 4A		0.01	0.03	0.81	0.10	0.05
Stage 4B		0.01	0.03	0.03	0.80	0.13

Assuming No Backward Transitions[a]

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.54	0.31	0.09	0.03	0.03	0.01
Stage 2		0.59	0.30	0.03	0.07	0.02
Stage 3			0.77	0.05	0.12	0.05
Stage 4A				0.84	0.12	0.04
Stage 4B					0.86	0.14

To From	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B	Dead
Stage 1	0.64	0.18	0.11	0.02	0.04	0.01
Stage 2		0.68	0.20	0.03	0.07	0.03
Stage 3			0.80	0.04	0.10	0.06
Stage 4A				0.85	0.10	0.05
Stage 4B					0.87	0.13

ALS = amyotrophic lateral sclerosis; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials.

[a] ALS is a progressive disease. These matrices assume that recorded improvements were misclassified and that patients continued in the same health state.

[b] Thakore et al.[7] presented two transition matrices: one based on the distribution of patients after three months and another based on the distribution of patients after six months. For ease of comparability, the six-month transition matrix was converted to a three-month matrix, assuming constant hazard rates.

Source: Thakore et al.[7] using the PRO-ACT database.

Table 18: Stage-Specific Direct Costs of Health Care for Patients With ALS (Excluding Edaravone)

	Stage 1	Stage 2	Stage 3	Stage 4A	Stage 4B
Annual costs	10,478	89,716	300,851	690,258	803,771

ALS = amyotrophic lateral sclerosis.

Note: Costs presented in 2017 Canadian dollars.

Source: Manufacturer's economic report, Table A-3.[3]

Table 19: Summary of Direct Health Care Costs for Patients With ALS

Study	Country (Setting)	Patient Characteristics	Reported Average Annual Cost	Currency-Year of Report	Annual Cost 2017 C$[a]
Van der Steen et al.[22]	Netherlands	Mixed cohort	15,756	2003 €	31,630
		ALSFRS items 0–20	24,444	2003 €	49,071
		ALSFRS items 20–30	16,488	2003 €	33,100
		ALSFRS items 30–40	13,188	2003 €	26,475
Lopez-Bastida et al.[23]	Spain	Mixed cohort	8,289	2004 €	16,693
		Low severity (no caregiver assistance)	6,517	2004 €	13,125
		High severity (requires caregiver assistance)	8,892	2004 €	17,908
Jennum et al.[25]	Denmark	Mixed cohort	14,268	2009 €	25,811
Schepelmann et al.[24]	Germany	Mixed cohort	14,980	2009 €	27,099
		Requires artificial ventilation	34,053[b]	2009 €	61,603
		No artificial ventilation	12,756[b]	2009 €	23,077
		Requires artificial nutrition	26,476[b]	2009 €	47,897
		No artificial nutrition	12,481[b]	2009 €	22,578
		Requires assistance with ADL	20,321[b]	2009 €	36,760
		No assistance with ADL	4,867[b]	2009 €	8,805
Meng et al.[32]	US (private insurance)	Mixed cohort	48,756	2010 US$	56,207
	US (Medicare)	Mixed cohort	54,612	2010 US$	62,958
Larkindale et al.[27]	US (private insurance)	Mixed cohort	30,934	2010 US$	35,661
	US (Medicare)	Mixed cohort	31,766	2010 US$	36,621
Connolly et al.[26]	Ireland	Mixed cohort	21,000	2011 €	31,451
Athanasakis et al.[33]	Greece	Mixed cohort	4,305	2013 €	6,256
Obermann et al.[34]	US	Single patient case study over 10 years	135,000 to 160,000	2013 US$	150,000 to 175,000
Nonoyama et al.[21]	Canada	ALS with home mechanical ventilation	60,504	2015 C$	62,320

ADL = activities of daily living; ALS = amyotrophic lateral sclerosis; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale.

Note: Costs presented in 2017 Canadian dollars.

[a] Currency was converted using average exchange rates for the year and then adjusted for inflation using the Canadian Consumer Price Index.

[b] Only costs for the overall cohort were stratified by direct and indirect sources (41% direct). The total costs (direct and indirect) reported for individuals in these subgroups were multiplied by 41% to estimate the direct costs only.

Source: Literature.

Table 20: Data Sources

Data Input	Description of Data Source
Efficacy	Study 19[9]
Natural history	Calibration conducted by the manufacturer assuming a relative risk of mortality by stage of disease observed in the PRO-ACT database[5] and with calibration targets being the health-state residency times and overall life expectancy observed in two relatively large ALS trials
Utilities	Article by Beusterien et al.[11]
Adverse events (indicate which specific adverse events were considered in the model)	Not included
Mortality	Captured through the natural history
Costs	Literature and Canadian sources
Drug	Manufacturer
Administration	Administration costs were underestimated
Adverse events	Not included
Health state	Derived by manufacturer

ALS = amyotrophic lateral sclerosis; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials.

Table 21: Manufacturer's Key Assumptions

Assumption	Comment
Patients progress through the stages of ALS and cannot move from stage 1 to stage 3/4A/4B or stage 2 to stage 4A/4B.	This does not reflect the natural history of ALS and this fact was considered in CADTH reanalyses.
The analyses are best conducted by considering the entire patient population (all ALS, at various stages) despite the heterogeneity of ALS, its progression, and the effect of edaravone.	CADTH considered analyses stratified by ALS stage in the reanalyses.
Treatment effect was assumed to be captured using a relative risk ratio, which is not constant over time.	Treatment effect is more appropriately estimated using hazard ratio, which was considered in CADTH reanalysis.
Administration costs would be fully covered [redacted].	[redacted]. There are, however, patients who may prefer treatment at care facilities or at home, and it is unclear whether the manufacturer would cover these costs.
Mapping of ALSFRS-R to King's Stage is appropriate.	While there is published information on the mapping algorithm between the two scales, this complicates the ability to validate the results of the clinical trials with that from the economic model.
Choice of health-state costs is appropriate.	This is unclear, as the costs selected by the manufacturer appear to be significantly higher than those reported in the literature. This was explored in the CDR reanalyses.
Exclusion of AEs and their associated costs is appropriate.	Unclear. As patient experience with edaravone increases, more information about AEs and their consequences may emerge. Where AEs require management with health care resources, this should be revisited, as it is likely to increase the ICUR for edaravone.

AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Manufacturer's Results

Table 22: Summary of Results of the Manufacturer's Base Case

	Edaravone	Standard of Care	Incremental
Life expectancy (in months)	24.0	21.9	2.1
Discounted (1.5%) health economic outcomes			
Pharmacy costs	$236,533	$8,026	$228,507
All other health care costs	$751,775	$757,806	−$6,031
Total costs	$988,308	$765,832	$222,476
Life-years	1.949	1.781	0.168
QALYs	0.966	0.852	0.114
Incremental cost-effectiveness ratio			
Cost per life-year gained			$1,326,365
Cost per QALY gained			$1,957,205

QALY = quality-adjusted life-year.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs and QALYs are probabilistic values from the manufacturer's submitted report and economic model submitted to CADTH.[3]

CADTH Common Drug Review Reanalyses

Table 23: Disaggregated Costs for the CDR Base Case Stratified by Initial ALS Health State

	Pharmacy Costs	All Other Health Care	Total
Stage 1			
Edaravone	394,054	140,463	534,517
Standard of care	14,329	135,437	149,767
Difference	379,724	5,026	384,750
Stage 2			
Edaravone	323,545	139,335	462,880
Standard of care	12,884	133,788	146,672
Difference	310,661	5,547	316,208
Stage 3			
Edaravone	270,622	129,534	400,156
Standard of care	11,420	126,107	137,527
Difference	259,202	3,427	262,630
Stage 4A			
Edaravone	221,931	150,503	372,434
Standard of care	12,020	143,915	155,935
Difference	209,911	6,588	216,499

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

Table 24: Impact of Each Major Change in the CDR Reanalysis

Percentage of Base Case	Incremental Cost-Effectiveness Ratio ($ per QALY Gained)				
	Manufacturer's Base Case[a]	Stage 1	Stage 2	Stage 3	Stage 4A
Manufacturer's model	1,957,000	1,351,000	2,299,000	4,970,000	26,022,000
Change to the ALS natural history transitions enabling progressive transitions to non-adjacent health states	2,172,000	1,533,000	2,059,000	3,479,000	4,340,000
Using a constant hazard rate and hazard rate–ratio approach for estimating effectiveness (HR = 0.665)	1,595,000	1,099,000	2,005,000	3,746,000	19,619,000
Revised treatment costs to include 13 treatment cycles per year	2,123,000	1,468,000	2,495,000	5,391,000	28,070,000
Revised costs for drug administration	2,126,000	1,474,000	2,498,000	5,388,000	27,928,000
Revised costs for non-drug ALS stage–stratified health care	2,031,000	1,422,000	2,414,000	5,159,000	24,983,000
Revised societal-perspective costs incurred by patients and families	2,097,000	1,481,000	2,496,000	5,300,000	25,020,000

ALS = amyotrophic lateral sclerosis; CDR = CADTH Common Drug Review; HR = hazard ratio; QALY = quality-adjusted life-year.

[a] Mixed population of patients (36% stage 1; 17% stage 2; 20% stage 3; 18% stage 4A; 9% stage 4B).

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