CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Sodium phenylbutyrate and ursodoxicoltaurine (Albrioza)

Indication: For the treatment of patients with amyotrophic lateral sclerosis (ALS)

Sponsor: Amylyx Canada

Recommendation: Reimburse with Conditions

Single Technology

CADTH

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sodium phenylbutyrate and ursodoxicoltaurine be reimbursed for the treatment of amyotrophic lateral sclerosis (ALS) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

There was evidence from the phase II, double-blind (DB), placebo-controlled CENTAUR study (N = 137) that treatment with PB-TURSO resulted in added clinical benefit for patients with a diagnosis of definite ALS who were within 18 months of symptom onset. There was a statistically significant improvement in rate of change in the ALS Functional Rating Scale – Revised (ALSFRS-R) total score with PB-TURSO corresponding to a between-group difference in change from baseline to week 24 of 2.32 points (95% confidence interval [CI], 0.18 to 4.47 points; P = 0.03). There was some uncertainty in the magnitude of the treatment effect due to the amount of missing data, with 75% of patients in the primary analysis population contributing data at week 24. Although there are no minimal important difference (MID) estimates available for the ALSFRS-R total score, the treatment effect was considered to be clinically meaningful according to clinical expert opinion. ALS is a rare, progressive, life-threatening disease for which there are no treatments to stop or reverse disease progression. Patients need treatments that significantly slow progression, help them maintain independence, and increase survival; PB-TURSO may meet some of these needs for some patients.

Using the sponsor submitted price for PB-TURSO and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for PB-TURSO was $2,086,658 per quality-adjusted life-year (QALY) compared with riluzole alone. At this ICER, PB-TURSO is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold in the Health Canada indication. CADTH notes the results of the analysis are driven by the high treatment cost of PB-TURSO (over $217,000 per patient annually). A reduction in price is required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. To be eligible for treatment with PB-TURSO, patients must meet all of the following: 1.1. have a diagnosis of definite ALS 1.2. have had ALS symptoms for 18 months or less 1.3. have an FVC of at least 60% of predicted value 1.4. not require permanent non-invasive ventilation or invasive ventilation	These patient characteristics are aligned with the patient selection criteria in the CENTAUR study. Although the study criteria used SVC, the clinical expert indicated that FVC and not SVC is used in clinical practice and the two values should be generally equivalent to each other. There is no evidence that PB-TURSO adds clinical benefit for patients who do not meet all of these conditions.	The revised El Escorial criteria were used to define definite ALS in the CENTAUR study.
Discontinuation		
2. Treatment with PB-TURSO should be discontinued if any of the following are met: 2.1. The patient requires invasive or permanent non-invasive ventilation 2.2. The patient becomes non-ambulatory and is unable to cut food and feed themselves without assistance, irrespective of whether a gastrostomy is in place	Once a patient requires invasive or permanent non-invasive ventilation, or is dependent for all activities of daily living, PB-TURSO no longer provides benefit as there are few surviving motor neurons.	—
Prescribing		
3. The patient must be under the care of a specialist with experience in the diagnosis and management of ALS.	This will ensure that PB-TURSO is prescribed for appropriate patients who are also receiving multidisciplinary care for ALS.	—
Pricing		
4. A reduction in price	The ICER for PB-TURSO is $2,086,658 when compared with riluzole. A price reduction of at least 98% would be required for PB-TURSO to be able to achieve an ICER of $50,000 per QALY compared to riluzole alone.	—
Feasibility of Adoption		
5. The feasibility of adoption of PB-TURSO must be addressed	At the submitted price, the budget impact of PB-TURSO is expected to be greater than $40 million in years 1, 2 and 3 if prescribed in the full Health Canada indication.	—

	Reimbursement Condition	Reason	Implementation Guidance
6.	The feasibility of adoption of PB-TURSO must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

ALS = amyotrophic lateral sclerosis; FVC = forced vital capacity; PB-TURSO = sodium phenylbutyrate and ursodoxicoltaurine; SVC = slow vital capacity.

Discussion Points

- CDEC noted that only a narrow population of patients with ALS, those with a diagnosis of definite ALS and within 18 months of symptom onset, was included in the CENTAUR study. Although the clinical expert indicated that there is no physiological or pharmacological reason to predict that patients in the other El Escorial diagnostic categories (i.e., probable ALS or possible ALS) would not respond to the treatment, CDEC considered the efficacy of PB-TURSO in patients not meeting the strict criteria to be unknown given the lack of evidence.

- There were no statistically significant differences for PB-TURSO versus placebo found for any secondary end points (including accurate test of limb isometric strength [ATLIS], slow vital capacity [SVC], and survival outcomes) in the CENTAUR study. Health-related quality of life and impacts on caregiver burden were not evaluated in the CENTAUR trial.

- Survival analyses conducted during the CENTAUR extension study suggested a benefit in median survival with PB-TURSO (median survival at the latest data cut-off: 23.5 months versus 18.7 months; hazard ratio [HR] = 0.64 [95% CI, 0.42 to 1.00]; P = 0.0475). However, there is a high degree of uncertainty in these results since there was no control for analyses at multiple time points, there was missing data for death equivalent events, and all patients received PB-TURSO in the extension study. As such, no conclusions regarding the impact of PB-TURSO on survival can be made at present.

- CDEC noted that patients with ALS require a multidisciplinary health care approach to managing their disease. Patient outcomes are more likely to be optimized if patients receive PB-TURSO in combination with coordinated care from other health professionals at centres with health care teams that have experience in managing patients with ALS.

- Most patients in the CENTAUR study were receiving concomitant riluzole and/or edaravone, which is reflective of the current standard of care in Canada. Therefore, CDEC considered it appropriate that PB-TURSO be given in addition to the current standard of care. CDEC also agreed with the clinical expert that patients should not have to demonstrate treatment failure with edaravone and/or riluzole before being able to access PB-TURSO. Currently available treatments for ALS have only a modest effect on disease progression and do not stop disease progression. The clinical expert advised that early intervention is important to preserve remaining motor function.

- The efficacy of PB-TURSO versus riluzole and edaravone is unknown due to the inability to perform a matching-adjusted indirect comparison (MAIC) with edaravone and the serious limitations of a post-hoc comparison of PB-TURSO and edaravone in the CENTAUR study.

- CDEC noted that the magnitude of the treatment effect reported in the CENTAUR study should be confirmed with a phase III study and that the Health Canada Notice of Compliance for PB-TURSO is conditional on the results of trials to verify its clinical benefit. The PHOENIX trial is an ongoing randomized, DB, phase III study evaluating the safety and efficacy of PB-TURSO versus placebo for 48 weeks in adults with ALS. The PHOENIX study population is broader than that of the CENTAUR trial allowing enrollment of patients with a diagnosis of definite ALS or clinically probable ALS and who are 24 months or less from symptom onset.

- The committee noted that the health economic reanalysis conducted by CADTH was based on more favourable assumptions regarding PB-TURSO efficacy than suggested by the sponsor. Given the high degree of clinical uncertainty, the incremental benefit derived from the CADTH reanalysis may overestimate the benefit derived from PB-TURSO.

Background

Sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO) has been approved by Health Canada for amyotrophic lateral sclerosis (ALS). Sodium phenylbutyrate is a pan-histone deacetylase inhibitor that ameliorates endoplasmic reticulum stress by upregulating chaperone proteins. Ursodoxicoltaurine ameliorates mitochondrial stress by reducing mitochondrial permeability and increasing the

apoptotic threshold of the cell. It is available as individual sachets, each containing 10 g of powder (3 g sodium phenylbutyrate and 1 g ursodoxicoltaurine) to be reconstituted in 250 mL of room temperature water and taken orally or administered via feeding tube within 1 hour of preparation. The recommended dose in the product monograph is 1 sachet daily for the first 3 weeks and 1 sachet twice daily thereafter.

Amyotrophic lateral sclerosis is a rare, incurable, neurodegenerative disease primarily affecting the nerve cells that control voluntary muscles. Deterioration of motor neurons leads to muscle weakness, muscle twitching, muscle tightness, and muscle atrophy. Later symptoms include shortness of breath, difficulty breathing, difficulty swallowing, and paralysis. Respiratory failure is the most common cause of death. It is estimated that there are 3,000 Canadians living with ALS and approximately 1,000 patients die from ALS each year with a similar number diagnosed every year in Canada. A review of Canadian data has estimated the annual incidence of ALS to be between 1.63 and 2.4 per 100,000 persons and prevalence to be 4.9 per 100,000 persons. The median survival time from symptom onset to death ranges from 20 to 48 months. Current treatments for ALS include riluzole and edaravone though no current therapies stop disease progression.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 RCT in adults with ALS

- A review of 1 extension study in adults with ALS

- Patients' perspectives gathered by 2 patient groups, ALS Society of Canada and ALS Action Canada

- Input from public drug plans that participate in the CADTH review process

- One clinical specialist with expertise diagnosing and treating patients with ALS

- Input from 1 clinician group, Canadian ALS Research Network

- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions for the review of PB-TURSO. The ALS Society of Canada conducted an online survey of 629 patients and caregivers from Canada, US, UK, Israel, and the Netherlands between November 10 and 24, 2021. A second patient group, ALS Action Canada, collected patients' experiences and opinions through email communications and Zoom meetings from members of their organization living in British Columbia, Alberta, Ontario, and Nova Scotia.

Both of the submitting patient groups described living with ALS as having an impact on every aspect of patients' lives as well as the lives of those around them. ALS Canada described the impact as "profound and pervasive". The submission spoke especially of the impact of patients' decline in ability (i.e., motor function, speech, and swallowing), making daily tasks such as self-care and feeding themselves difficult and eventually impossible, leading to a strongly felt loss of independence. Managing the condition is demanding on patients and caregivers, requiring several hours a day for treatments, exercising for legs and arms, breathing exercises, a constant regimen of drugs and supplements, and appointments. As the disease progresses people living with ALS become increasingly reliant on those around them and caregivers take on a significant role in assisting their loved ones. Both patient group submissions stressed the broader toll on caregivers – pervasive feelings of overwhelming grief and struggles with mental health, including stress, anxiety, and helplessness and hopelessness. Although some patients felt that currently available medications (edaravone and riluzole) appeared to slow disease progression, help maintain motor function, and increase survival, in general the submitting patient groups noted that these existing therapies fall short of having a significant impact on the outcomes desired by patients – slowing the progress of their disease and increasing lifespan A limited number of patients who had access to PB-TURSO felt the main benefits were slowed disease progression and maintained motor function. A few respondents reported side effects that were mostly gastrointestinal related and taste disturbances. Patients and caregivers emphasized the importance of and urgency for

access to new treatments that significantly slow progression, help patients maintain their independence, reverse symptoms, increase survival, and do not add to the disease treatment burden.

Clinician input

Input from clinical expert consulted by CADTH

The clinical expert highlighted that there are no available treatments that stop or reverse disease progression, reduce symptom severity, minimize adverse events, and improve HRQoL. Riluzole may have a modest survival benefit. It was emphasized that current treatments demonstrate very modest benefits with slowing progression; however, ALS remains a terminal disease. Due to the progressive nature of ALS and low survival beyond 5 years after diagnosis, the clinical expert indicated that it is reasonable to target all potential pathological pathways as early as possible. Riluzole, edaravone, and PB-TURSO act on different pathways and targets in the body and may be used simultaneously with a 1- to 2-week interval between starting a new treatment to assess tolerance and side effects. The clinical expert explained that it is important to start treatment early to spare healthy neurons and preserve muscle function in affected areas of the body.

The clinical expert noted that all patients diagnosed with ALS would be suitable for treatment with PB-TURSO. The expert suggested that patients who are most suitable for treatment be decided based on clinician judgement rather than functional rating scores or pulmonary function tests since patients may have limited access to ALS specially clinics. Per input from the clinical expert, ALS is clinically heterogenous and the rate of progression is individual, which complicates monitoring outcomes and defining a response to therapy. According to the Canadian Best Practice Recommendations, patients should be routinely monitored every 3 to 4 months.

The clinical expert indicated that patients with advanced disease may not benefit from treatment with PB-TURSO though the definition of advanced disease may vary among clinicians and differ between clinicians and patients. It was suggested that treatment discontinuation could be considered for patients with advanced disease who are fully dependent for their activities of daily living, walking, transfers, and feeding. Changes to a patient's goals of care or a desire to discontinue a medication should also be considered. It would be appropriate for a neurologist or physiatrist with experience caring for patients with ALS to prescribe PB-TURSO though all patients should have a multidisciplinary care team and be followed by an ALS clinic.

Clinician group input

Input was received from the Canadian ALS Research Network (CALS), which consisted of 10 CALS members from across Canada. The clinician group input was similar to that given by the clinical expert consulted by CADTH.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
Patients were randomized 2:1 to PB-TURSO or matching placebo. Patients could remain on riluzole and/or initiate or remain on edaravone. Placebo is likely an appropriate comparator in this treatment space, as PB-TURSO could be considered early on in the disease course and could be considered as an add-on to riluzole or edaravone. Can CDEC comment on the relevant comparator?	CDEC agreed with the clinical expert that placebo was the appropriate comparator since PB-TURSO is expected to be an add-on treatment to the current standard of care (riluzole and/or edaravone).
In CENTAUR, a group of patients were allowed to initiate edaravone as well as PB-TURSO. For those patients who were newly initiated on edaravone, it is unclear what benefit was derived from edaravone versus PB-TURSO.	Patients in both treatment groups in the CENTAUR trial were permitted to initiate edaravone treatment. CDEC noted that preplanned subgroup analyses with adequate sample sizes would have been needed to separate out the effect of PB-TURSO from that of edaravone.
Considerations for Initiation of Therapy	

Implementation Issues	Response
Clinical trials used the revised El Escorial criteria; it is noted that these are relevant for clinical trials, but are not widely used in clinical practice. CENTAUR enrolled patients with definite ALS, based on the El Escorial criteria. The sponsor's reimbursement request does not restrict reimbursement only for patients with definite ALS as per the El Escorial criteria.	According to the clinical expert, the use of definite ALS by the El Escorial criteria was based on clinical trial design decisions (to determine a rapid answer as to whether the drug was potentially effective). By restricting the inclusion criteria to a definite diagnosis of ALS by the El Escorial criteria and be less than 18 months from ALS symptom onset, the trial would be restricted to patients who progress relatively rapidly. Restricting a trial to rapidly progressive patients would mean that less time would be required to demonstrate a change in rate of progression, as compared to a wider population of patients with ALS. There is no physiological or pharmacological reason to predict that patients at other levels of the El Escorial diagnostic criteria (i.e., "probable" or "possible") would not respond to the treatment. CDEC agreed with the clinical expert.
The sponsor notes that earlier access results in better treatment outcomes, and patients should not have to try alternative therapies before accessing PB-TURSO. All jurisdictions list edaravone with criteria. Riluzole is the other marketed ALS treatment. Some jurisdictions list it with criteria, others do not list it, and still others list it as a full benefit. Five of the 6 jurisdictions listing with criteria require an FVC of more than 60%.	According to the clinical expert, it is expected that PB-TURSO would be offered as add-on therapy in addition to riluzole and/or edaravone. CDEC agreed with the clinical expert.
The CENTAUR trial looked at a measure called slow vital capacity (SVC). How does SVC relate to FVC? Is SVC used in clinical practice?	The clinical expert stated that it is not standard practice to measure SVC in ALS clinics in Canada, though its use may vary among clinicians. According to the expert, it is more common to measure FVC to assess respiratory function in clinical practice. It was also noted that SVC is felt to be generally equivalent to FVC. CDEC agreed with the clinical expert.
The reimbursement criteria for edaravone and riluzole require FVC scores above a certain threshold at the time of initiation. The edaravone reimbursement criteria require patients to have probable or definite ALS. The CENTAUR trial for PB-TURSO enrolled patients with definite ALS.	CDEC note the differences between the reimbursement criteria for edaravone and riluzole and the eligibility criteria for the CENTAUR study with respect to patient population. CDEC considers it most appropriate to align the reimbursement criteria for PB-TURSO with the patient population studied in the CENTAUR trial.
Considerations for continuation or renewal of therapy	
ALS disease progression is measured using the ALSFRS-R, which consists of 4 domains measuring 12 different activities of daily living in each domain. Each item score ranges from 0 to 4 with a maximum score of 48, which indicates normal function. As the disease is progressive in nature what would be reasonable reduction in ALSFRS-R score that signifies benefit with treatment at 6 months? At the end of the 6-month randomized study period, there was a difference of 2.32 points between groups in the ALSFRS-R estimate; however, both groups experienced decline in the ALSFRS-R estimate. It will be difficult to withdraw therapy if patients are deteriorating despite therapy.	The clinical expert stated that, due to the progressive nature of ALS, all patients are expected to decline over the course of the disease. Currently, there are no available therapies to stop or reverse disease progression and available treatments only show modest effects in slowing progression. The clinical expert indicated that the average decline among patients with ALS is approximately 1 point per month during the course of the disease although decline may slow towards the end stages of the disease. It was noted that patients will decline faster or slower than this average without treatment, which makes comparisons to the average rate of decline challenging. The clinical expert explained that clinicians are unlikely to have an accurate reading of a patient's rate of decline based on ALSFRS-R scores before treatment and on-treatment to compare on an individual patient level.

Implementation Issues	Response
	CDEC agreed with the clinical expert and did not consider it practical to require assessment of treatment response based on the ALSFRS-R.
Considerations for discontinuation of therapy	
Clearly defined discontinuation criteria would be helpful. Given the progressive nature of the disease it will be difficult to discontinue coverage of therapy.	Per Canadian Best Practice Recommendations, the clinical expert noted that patients with ALS should be routinely monitored every 3 to 4 months. PB-TURSO could be continued until the goals of treatment change and become more palliative, or the patient requires total care or near-continuous ventilation as this indicates there are few surviving motor neurons and the drug no longer provides benefit. The clinical expert indicated that specific examples for discontinuation could include: • BiPAP support for > 20 hours per day • Wheelchair dependency AND need to be fed by a caregiver (i.e., dependent for all activities of daily living). CDEC noted the need for clearly defined discontinuation criteria and considered the clinical expert's specific examples.
In the CENTAUR trial, patients were treated within 13.5 months of diagnosis. Is it necessary to start therapy early for patients to demonstrate a beneficial response?	CDEC agreed with the clinical expert that early intervention is important to prevent motor neuron death towards the goals of slowing progression of ALS and preserving muscle function.
Consider consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space. See comment above regarding renewal criteria.	CDEC considered this comment in their deliberations, noting that the patient population and clinical outcomes differed among the studies for the other ALS drugs and that this could affect renewal and discontinuation criteria.
Considerations for prescribing of therapy	
The dosing regimen for PB-TURSO may be preferred to that for edaravone, which requires an IV infusion to be given over a 60-minute period according to the following schedule: • Initial treatment cycle with daily dosing x 14 days, then 14 days off. • Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.	CDEC and the clinical expert agreed with this statement and CDEC considered it in their deliberations.
PB-TURSO can be administered orally or per feeding tube which is an important consideration in patients with ALS.	CDEC and the clinical expert agreed with this statement and CDEC considered it in their deliberations.
Some jurisdictions may have limited access to specialists experienced in diagnosing ALS and this may lead to delay in treatment initiation. In the CENTAUR trial, patients had an average of 13.5 months since symptom onset and 6 months since diagnosis before patients were enrolled in the study. In some jurisdictions, it is likely that access to specialists and diagnosis exceeds this timeframe.	The clinical expert stated that most jurisdictions in Canada should be able to confirm a diagnosis of ALS within 12 to 18 months. Access to specialist diagnosis should not be an issue, particularly since the Canadian Best Practice Recommendations have required an appointment for confirmation of a diagnosis of ALS within 4 weeks of a referral to a specialist. CDEC agreed with the clinical expert.
In the CENTAUR trial, patients could remain on therapy with riluzole and edaravone.	CDEC agreed with the clinical expert that it is expected that PB-TURSO would be offered as add-on therapy in addition to riluzole and/or edaravone.
Edaravone criteria specify patients should have probable or definite ALS. The CENTAUR study enrolled patients with definite ALS. Conditions for coverage of edaravone require patients to have scores of at least 2 points on each item of the ALSFRS-R; have ALS symptoms for 2 years or less; and have an FVC	The clinical expert consulted on this review emphasized that there are no available treatments that have a proven ability to stop disease progression. Those that are available only modestly slow disease progression. Patients should not have to demonstrate treatment failure before being able to access another therapy.

Implementation Issues	Response
of greater than or equal to 80% predicted. In addition, patients must not require permanent non-invasive or invasive ventilation. Consistency of criteria depends on what the place in therapy for this product is determined to be.	CDEC agreed with the clinical expert and noted that the reimbursement criteria for PB-TURSO would have to reflect the available evidence (i.e., the CENTAUR study).
Generalizability	
The clinical trial was relatively small given the incidence of the disease. Approximately 1 in 50,000 people in Canada is diagnosed with ALS each year. A total of 137 patients were enrolled in the CENTAUR study. The study was conducted across a number of states in the US and enrolled patients with definite ALS based on the revised El Escorial criteria. Patients with probable and possible ALS may also seek treatment given the limited treatment options which exist. The RCT did not show any survival benefit. Survival was assessed in the open label extension. It would be helpful if CDEC can comment on the methodology. The RCT is a 6-month, phase II trial, with a primary outcome of assessing the safety and tolerability of PB-TURSO. The primary efficacy end point was ALSFRS-R total score.	The clinical expert explained that it is highly unlikely that a 6-month trial could demonstrate survival benefit due to the natural history of the disease. The clinical expert added that it is much more likely that a survival benefit be seen over a 12- or 18-month trial. CDEC agreed with the clinical expert. Regarding the survival analyses during the CENTAUR open-label extension, CDEC considered the evidence to be supportive of the clinical benefit of PB-TURSO. CDEC agreed with the CADTH assessment of the open-label extension limitations and of the RPSFT model results (namely, that conclusions could not be drawn on the RPSFT model results).
Patients will advocate for early access to the drug as 80% of patients with ALS die within 2 to 5 years of being diagnosed.	CDEC and the clinical expert agreed with this statement.
System and economic issues	
Duration of treatment was assumed by the sponsor to be the same as edaravone in the budget impact analysis. The sponsor is claiming that PB-TURSO has a survival benefit, whereas edaravone does not. Therefore, treatment duration should not be equivalent. The sponsor's budget impact analysis assumed that all patients would be receiving riluzole. This is unlikely the case.	The clinical expert indicated that the majority of patients will be on riluzole. Some patients who do not tolerate riluzole could be tried on PB-TURSO. However, it would be extremely unusual to have a patient refuse riluzole or have a medical contraindication to riluzole and be prescribed PB-TURSO. CDEC agreed with the clinical expert.
PB-TURSO will likely be used as add-on therapy (in addition to riluzole and edaravone), therefore increasing the overall treatment cost of ALS significantly.	CDEC and the clinical expert agreed with this statement.
There may be some patients who are on the product through the SAP at the time of Health Canada approval. These patients may have to transition to another method of coverage once the drug is approved by Health Canada.	CDEC and the clinical expert agreed with this statement.
Generic versions of riluzole are now available. These are listed in at least 1 jurisdiction at 35% of the price of the brand-name drug.	CDEC considered this in their deliberations and noted that there is no direct or indirect comparative evidence for PB-TURSO versus riluzole or edaravone to inform on place in therapy.
What is an appropriate time horizon to assess cost-effectiveness of this drug? The manufacturer used a Markov state-transition model to describe the progression of ALS over a lifetime horizon (10 years). Is 10 years an appropriate timeframe?	The clinical expert felt 10 years would be a reasonable timeframe. CDEC agreed with the clinical expert.

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Function Rating Scale – Revised; CDEC = Canadian Drug Expert Committee; FVC = forced vital capacity; PB-TURSO = sodium phenylbutyrate and ursodoxicoltaurine; RCT = randomized controlled trial; RPSFT = rank-preserving structural failure time; SVC = slow vital capacity.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

The CENTAUR trial was a phase II, multi-centre, double blind (DB), placebo-controlled RCT to assess the safety, tolerability, and efficacy of PB-TURSO in adult patients with ALS. One sachet of medication was taken orally or via feeding tube once daily for the first 3 weeks and, if tolerated, 1 sachet twice daily thereafter. The CENTAUR trial was conducted at 25 Northeast ALS Consortium (NEALS) centres in the US and included 137 patients. Patients were randomized in a 2:1 ratio to receive either PB-TURSO and SOC (n = 89) or matching placebo and SOC (n = 48) for the duration of the 24-week DB treatment period. Standard of care included concomitant riluzole and/or edaravone. The study design consisted of (i) a screening period of up to 42 days, (ii) a DB treatment period of 24 weeks with study evaluations taking place every 3 weeks, and (iii) a follow-up for up to 4 weeks. Patients who discontinued early from the study were asked to return to the study site for final safety assessments. After completing the DB trial, patients could enroll in the 132-week open-label extension (OLE) phase.

The primary safety outcome of the CENTAUR study was to confirm the safety and tolerability of PB-TURSO while the primary efficacy outcome was the rate of change (slope) of disease progression as measured by the ALSFRS-R. Secondary outcomes included in the CADTH review protocol were the accurate test of limb isometric strength (ATLIS) for measuring isometric muscle strength, slow vital capacity (SVC) percent predicted normal (PPN) for respiratory function, and survival (defined as death, tracheostomy or permanent assisted ventilation) outcomes.

Patients had to have a diagnosis of definite ALS, be within 18 months of symptom onset, and have greater than 60% predicted normal SVC. The mean age of patients in the CENTAUR trial was 57.5 years (standard deviation [SD] = 9.50 years). Most patients were male (68.9%) and most patients were White (94.8%). The mean rate of disease progression (del-FS) prior to study entry was 0.95 points per month (SD = 0.43 points per month) in the PB-TURSO group and 0.93 points per month (SD = 0.60 points per month) in the placebo group. In general, mean ALSFRS-R total and domain scores were similar between the treatment groups as were mean SVC measurements. Mean ATLIS scores were numerically higher for those in the PB-TURSO group compared to the placebo group. The use of riluzole and/or edaravone at or prior to study entry was overall more common in the placebo group.

Efficacy Results

The primary efficacy outcome was the rate of change (slope) of disease progression as measured by the ALSFRS-R total score in the modified intent-to-treat (mITT) population. The slope for the ALSFRS-R total score was –1.24 points per month for the PB-TURSO group and –1.66 points per month for the placebo group. The treatment difference was 0.42 points per month (95% confidence interval [CI], 0.03 to 0.81 points per month; P = 0.03) comparing the PB-TURSO versus placebo groups. The mean change from baseline to Week 24 was –6.86 points (SE = 0.66 points) and –9.18 points (SE = 0.88 points) in the PB-TURSO and placebo groups, respectively. Overall, the difference in change from baseline to Week 24 between the PB-TURSO and placebo groups was 2.32 points (95% CI, 0.18 to 4.47 points; P = 0.03). For the per-protocol population, the difference comparing the PB-TURSO group to the placebo group was 2.54 points (95% CI, 0.28 to 4.81 points; P = 0.03). A prespecified sensitivity analysis was conducted for the missing at random assumption which resulted in a difference of 1.87 points (95% CI, 0.06 to 3.69 points) for PB-TURSO versus placebo. According to the clinical expert consulted for this review, a difference of at least 2 points over a period of 6 months for most ALS patients would be considered clinically meaningful if found to be reproducible through additional studies. Additionally, a change of 20% to 25% in the slope of ALSFRS-R was considered "at least somewhat clinically meaningful," according to surveyed clinical experts.

The first outcome in the testing hierarchy was the ATLIS total score. The mean changes from baseline to Week 24 were –16.72% (SE = 1.05%) and –19.54% (SE = 1.45%) for the PB-TURSO and placebo treatment groups, respectively. Overall, the difference comparing PB-TURSO versus placebo was 2.82% (95% CI, –0.67% to 6.31%; P = 0.11) at Week 24. Since the result was not statistically significant, statistical testing was stopped at the first outcome in the testing hierarchy and all subsequent P values were considered nominal (i.e., not adjusted for multiple testing). The differences from baseline to Week 24 for SVC PPN were –17.11% (SE = 1.70%) and –22.22% (SE = 2.32%) for the PB-TURSO and placebo groups, respectively. Overall, the difference comparing PB-TURSO versus placebo was 5.11% (95% CI, –0.54% to 10.76%) at Week 24. A total of 6 death or death equivalent events

occurred based on the mITT population resulting in a hazard ratio (HR) of 0.63 (95% CI, 0.11 to 3.92) for PB-TURSO versus placebo treatment groups.

Harms Results

The primary safety outcome of the CENTAUR study was to confirm the safety and tolerability of PB-TURSO. Overall, 86 patients (96.6%) in the PB-TURSO group and 46 patients (95.8%) in the placebo group experienced at least 1 treatment emergent adverse event (TEAE) during the CENTAUR trial. The 3 most frequently reported TEAEs in the PB-TURSO group were falls, diarrhea, and muscular weakness. In total, 23 serious adverse events (SAEs) were reported in 11 patients (12.4%) from the PB-TURSO group and 8 patients (16.7%) from the placebo group. The SAEs reported in more than 1 patient included respiratory failure, bacteremia, and nephrolithiasis. Overall, 18 patients (20.2%) from the PB-TURSO group and 5 patients (10.4%) from the placebo group withdrew from the study medication due to a TEAE. The most frequently reported reasons were due to diarrhea (5.6%) in the PB-TURSO group (versus 0 in the placebo group) and respiratory failure (6.3%) in the placebo group (versus 0 in the PB-TURSO group). There were 7 deaths reported during the CENTAUR trial in the safety population: 5 patients in the PB-TURSO group due to respiratory failure or respiratory arrest (3 patients), subdural hematoma (secondary to a fall; 1 patient), and diverticular perforation (1 patient) compared to 2 patients in the placebo group, both due to respiratory failure or respiratory arrest. The safety population included 2 additional patient deaths that were excluded from the mITT population.

Notable harms considered relevant to this review included gastrointestinal adverse events (AEs), neurological AEs, respiratory AEs, and taste disturbances. Frequently reported (in at least 5% of patients) gastrointestinal AEs that occurred more often among patients who received PB-TURSO included diarrhea (21.3% versus 16.7%), nausea (18.0% versus 12.5%), salivary hypersecretion (11.2% versus 2.1%), and abdominal discomfort (5.6% versus 0%). Neurological AEs occurring in at least 5% of patients such as dizziness were more frequent among patients who received PB-TURSO (10.1% versus 4.2%). Respiratory AEs that were reported in at least 5% of patients and were more common in patients who received PB-TURSO included dyspnea (10.1% versus 8.3%). Dysgeusia, or taste disturbance, occurred in 3.4% of patients who received active treatment compared to 2.1% of patients who received placebo. Investigators were instructed not to capture medication bad taste as an AE and instead, record issues with oral administration if there was a clinically untoward effect such as burning, vomiting, or anxiety.

Critical Appraisal

The key limitation was that the CENTAUR trial was a phase II trial with a small number of patients and a short duration. There were large proportions of patients who discontinued from the study and the number of patients available for the analysis at 24 weeks varied largely from the number of patients randomized at baseline. All efficacy outcomes had missing data, including the ALSFRS-R total score, at Week 24 due to patients discontinuing from the study (23% of the randomized population) leading to uncertainty in the results. For the ALSFRS-R instrument, information on its responsiveness to change and MID estimates were not found in the literature though estimates of what would be clinically meaningful based on clinical expert opinion are available. Survival data were limited by the small number of patients and were immature at the end of 6 months due to few events having occurred. The low frequencies for SAEs, withdrawals due to AEs (WDAEs), and deaths, due to small sample size and short duration, as well as the missing data available for analysis at 24 weeks compared to baseline made it difficult to draw any firm conclusions from these results.

All the study centres were in the US which limits the generalizability to Canadian practice on the basis of differences in health care provisions. The criteria of a definite ALS diagnosis within 18 months of symptom onset were very restrictive since they require patients to have a high level of symptoms that many patients would not meet within 18 months. These limitations prevented the capture of information for patients who are progressing slowly and may benefit from treatment with PB-TURSO. The clinical expert identified specific exclusion criteria that may also be restrictive: poorly controlled arterial hypertension (systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg) at screening, history of cholecystectomy, and exposure to antacids containing aluminum hydroxide or aluminum oxide within 2 hours of administration of PB-TURSO. Overall, the safety and efficacy of PB-TURSO are unknown outside of the CENTAUR study population. Patient-reported outcomes such as those measuring ALS symptoms or HRQoL were not included in the CENTAUR trial and little is known about the impact of PB-TURSO from the patient perspective.

Indirect Comparisons

Description of studies

Due to the lack of head-to-head comparisons between PB-TURSO and other ALS medications, the sponsor submitted a feasibility assessment for conducting a matching-adjusted indirect comparison (MAIC) to compare the relative efficacy of PB-TURSO to edaravone. In total, 1 RCT for PB-TURSO (the CENTAUR trial) and 2 RCTs for edaravone (Study 16 and Study 19) were included in the assessment. The sponsor stated that Study 16 and Study 19 were "sufficiently homogenous" for the data to be pooled using standard methods. The primary end point of the analysis was the difference between PB-TURSO and edaravone for the mean change in the ALSFRS-R total score from baseline to Week 24.

There were notable differences between the studies in terms of study design (e.g., location, pre-baseline observation period, and eligibility criteria) and baseline characteristics for sex, site of onset, duration of disease, ALSFRS-R baseline score, del-FS at baseline, proportion of patients with a definite ALS diagnosis, FVC or SVC at baseline, and use of riluzole or edaravone at baseline.

Efficacy Results

Adjustments were made for the following covariates: rate of disease progression (del-FS), baseline ALSFRS-R score, duration of disease, baseline FVC or SVC, and concomitant riluzole use at baseline. After matching to the pooled Study 16/19 data, the effective sample size of the CENTAUR trial was reduced from an original 135 patients to 24.8 patients. After adjusting for baseline edaravone use, the effective sample size was further reduced to 3.4 patients. The large reduction in effective sample size indicated the study populations were substantially different from one another and that it was not reasonable to conduct a MAIC using these populations. The sponsor's analysis identified del-FS to be the main reason for the reduction in effective sample size which was also considered to be the most clinically important covariate.

Critical Appraisal

The CADTH review team agreed that the reduction in effective sample size after adjustments indicated that there were substantial differences between the populations and that it would not be reasonable to compare the treatments between the CENTAUR trial and the pooled Study 16/19 data.

Other Relevant Evidence

Description of studies

The OLE of the pivotal CENTAUR trial provided long-term safety and efficacy evidence for PB-TURSO. In total, 90 patients enrolled in the OLE and those who were randomized to placebo in the DB phase received PB-TURSO in the OLE. The primary end point was long-term safety and patients were analyzed based on whether they received PB-TURSO during both DB and OLE phases or placebo and PB-TURSO during the DB and OLE phases, respectively. The secondary end points were for survival (hospitalization, tracheostomy, permanent assisted ventilation, death), ALSFRS-R, ATLIS, and SVC. Patients were analyzed based on if they were randomized to PB-TURSO or placebo in the CENTAUR study. The survival analysis was expanded following database lock and unblinding to treatment assignment to include information on death events obtained via a vital status sweep for all patients randomized in the main trial with data cut-offs of February 29, 2020 and July 20, 2020.

A post-hoc analysis of the CENTAUR trial was conducted to compare the relative efficacy of PB-TURSO to edaravone to support the sponsor's pharmacoeconomic model. The main subgroups of interest were patients who received PB-TURSO without edaravone and placebo with edaravone. The primary end point was the rate of change (slope) in ALSFRS-R total score from baseline to Week 24 using a shared-baseline mixed-effects model and the secondary end point was similar but using a change from baseline approach.

A second post-hoc analysis was performed on the survival data from patients in the CENTAUR trial up to 35 months post-baseline comparing the effect of switching treatments, i.e., placebo to PB-TURSO. In total, 34 of the 48 patients (71%) who received placebo during the DB phase enrolled in the CENTAUR OLE and began receiving PB-TURSO. The sponsor noted that any beneficial effect on overall survival of PB-TURSO over placebo in the absence of a switch will be underestimated in the pre-specified intent-to-treat (ITT) analysis. The overall survival end point was defined as all-cause mortality. The main objective of the analysis was to model

what the overall survival of patients in the CENTAUR trial may have been if patients from the placebo group had not switched treatments and received PB-TURSO. A rank preserving structural failure time (RPSFT) model was used and it was assumed that the treatment effect was consistent regardless of when it was given during the study, i.e., at randomization or upon enrollment to the OLE.

Efficacy Results

In the CENTAUR OLE trial, median survival for the ITT population was 25.0 months (95% CI lower bound = 20.8 months; upper bound not reached) and 18.5 months (95% CI lower bound = 14.9 months; upper bound not reached) for the PB-TURSO and placebo groups, respectively, yielding an HR of 0.56 (95% CI, 0.34 to 0.93) for death events at the July 20, 2020 data cut-off date. For death or death equivalent events, the median survival was 23.2 months (95% CI lower bound = 19.5 months; upper bound not reached) and 18.2 months (95% CI, 14.9 to 23.1 months) for the PB-TURSO and placebo groups, respectively, yielding an HR of 0.57 (95% CI, 0.35 to 0.93) at the July 20, 2020 data cut-off date. Based on the clinical study report with a data cut-off for March 1, 2021 which contains updated survival data, the median survival was 23.5 months and 18.7 months for patients randomized to PB-TURSO and placebo, respectively, resulting in an HR of 0.64 (95% CI, 0.42 to 1.00; P = 0.0475). At this cut-off, 94 death events were reported (69% of the ITT population) with 1 patient lost to follow-up. The FDA noted in the Combined FDA and Applicant Briefing Document for the March 30, 2022 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee that, using the likelihood ratio test specified in the survival statistical analysis plan, the HR is 0.64 with a P value of 0.0518. Further, the FDA also noted that with the inclusion of 5 additional death events captured following the March 1 cut-off, the HR is 0.70 with a P value of 0.1109. However, it was unclear how this was determined and the analysis would not have been from a planned data cut-off.

The treatment group differences (patients randomized to PB-TURSO versus placebo) were 4.23 points (95% CI, 0.56 to 7.90 points) for the ALSFRS-R total score, 6.20% (95% CI, 0.01% to 12.39%) for the ATLIS total score, and 10.66% (95% CI, 0.63% to 20.69%) for SVC.

In the first post-hoc analysis, the estimated effect sizes between patients in the PB-TURSO without edaravone group and patients in the placebo with edaravone group varied from 2.62 points to 3.22 points using a shared-baseline approach. The secondary end point results (using a change from baseline approach) varied from 3.61 points to 4.41 points.

For the second post-hoc assessment's primary and sensitivity analyses (with and without recensoring), the acceleration factor estimates were all less than 1 indicating that PB-TURSO had a beneficial effect on overall survival. Using the RPSFT model without recensoring, the median overall survival was approximately 13.5 months for the placebo group with a HR of 0.34 (95% CI, 0.13 to 0.87). When recensoring was applied, the median overall survival was approximately 15.2 months for the placebo group with a HR = 0.40 (95% CI, 0.18 to 0.88).

Harms Results

The proportion of patients who reported the most common AEs (5% or greater) was higher in the group who received placebo in the DB phase (PA group; 82.4%) compared with the group who received PB-TURSO in the DB phase (AA group; 73.2%). The most common AEs were falls, nausea, and diarrhea. The incidence of SAEs was also higher in the PA group (20.6% versus 14.3%). The percentage of patients withdrawing from the study due to AEs was higher in the PA group (29.4%) than the AA group (10.7%). Five patients (14.7%) in the PA group and 2 patients (3.6%) in the AA died prior to Week 24 in the OLE study. The reasons were respiratory failure, disease progression or ALS, and cardiac arrest. The most common notable harms were nausea (17.6% in PA group versus 12.5% in AA group) and diarrhea (20.6% versus 8.9%). Dysgeusia was reported only in the PA group (2.9%). At the latest data cut-off, the numbers of patients reporting at least 1 AE were 32 (94.1%) patients in the PA group and 49 (87.5%) patients in the AA group with notable increases in the percentage of patients reporting respiratory failure, dyspnea, constipation, and pneumonia. Further, 13 (38.2%) and 18 (32.1%) patients experienced at least 1 SAE in the PA and AA groups, respectively.

Harms were not assessed in either of the 2 post-hoc analyses.

Critical Appraisal

Given the nature of OLE studies, there is bias that impacts how the results are interpreted such as the lack of blinding during the OLE phase, lack of control group, and selection bias for patients who successfully completed the main trial. Also, there were large

proportions of study discontinuations and it is possible that treatment assignment from the main trial was deduced for some patients based on the differences in gastrointestinal AEs between groups. All efficacy end points are secondary outcomes and it is not possible to make definitive conclusions based on the available data. Although vital status was available for all patients but 2 from the main trial ITT population, death equivalent events outside of the study were not captured, contributing uncertainty to the death or death equivalent composite end point. Due to the crossover in the OLE, assuming any effect of PB-TURSO on survival is beneficial, bias from treatment switching would be against PB-TURSO. The generalizability issues identified for the DB phase regarding patient characteristics and outcome measures also apply to the OLE.

A key limitation to the post-hoc analyses was that neither assessment was pre-specified, and therefore they should be viewed as hypothesis-generating. Specific to the first post-hoc analysis, defining treatment groups by whether a patient received edaravone meant that the benefits of randomization were lost for these comparisons. Additionally, the groups included only a subset of the mITT population and sample sizes were small as a result. Given the serious limitations, it is not possible to make any conclusions on how treatment with PB-TURSO compared to edaravone. In the second post-hoc analysis, the overall survival assessment relied on the assumption of constant treatment effect associated with the RPSFT model to accommodate crossovers from placebo to PB-TURSO in the OLE. The validity of the main assumption of the RPSFT method is unknown and no conclusions can be drawn from the RPSFT model results.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	People with amyotrophic lateral sclerosis (ALS)
Treatment	Sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO)
Submitted price	Powder-filled sachet containing sodium phenylbutyrate, 3 g; ursodoxicoltaurine, 1 g: $306.71 per sachet
Treatment cost	The annual cost of PB-TURSO, as calculated by CADTH, was $217,459 in the first year of treatment and $223,900 in subsequent years.
Comparators	• Riluzole • Edaravone • Best supportive care (BSC) consisting of symptomatic disease management
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	• The target population was based on the phase 2 CENTAUR trial • Transition probabilities between health states were derived from a previously published economic evaluation, Thakore et al., (2020) • A rate ratio for PB-TURSO compared to riluzole derived from a post-hoc analysis of the CENTAUR trial was applied to the transition probabilities for riluzole to model comparative efficacy
Key limitations	• The sponsor assumed that patients receiving PB-TURSO would also experience the added efficacy of riluzole without the associated costs. Furthermore, upon discontinuing PB-TURSO patients retained the efficacy of riluzole for their lifetime. This assumption was not applied to the riluzole treatment arm. • The sponsor's model structure is based on the Fine'til 9 (FT9) staging system which is not used in clinical practice and may not adequately represent the natural history of ALS. • The sponsor assumed 100% of patients will discontinue PB-TURSO at 11 months. Given that there are no explicit stopping rules for this therapy and treatment will be given until disease progression or intolerability there is no justification to impose a strict time-based stopping rule.

Component	Description
	• The sponsor assumes a higher discontinuation rate for PB-TURSO compared to the other treatments, an assumption that would mean PB-TURSO is either less tolerable or less effective. This contradicts how the sponsor has modelled adverse events and progression rates for PB-TURSO. • Due to the sponsor's model structure, patients in FT9 Stage 4 do not incur any benefit with PB-TURSO while still incurring drug acquisition and healthcare costs. • As the adverse events included in the sponsor's model are also a product of disease progression, inclusion of separate costs and disutilities for these events potentially double counts this element of the analysis.
CADTH reanalysis results	• The CADTH reanalysis addressed the above limitations by: including drug costs for riluzole for patients on PB-TURSO; assuming patients follow BSC transition probabilities upon discontinuing PB-TURSO; removing the maximum time on therapy for PB-TURSO; equating the discontinuation rates; excluding AEs related to disease progression; and, moving patients in baseline Stage 4 to Stage 3. • The CADTH reanalysis resulted in an ICER for PB-TURSO versus riluzole of $2,086,658 per QALY (inc. costs: $285,060; inc. QALYs: 0.137), with a 0% probability of being cost-effective at a $50,000 per QALY threshold. CADTH reanalyses suggest that price reductions of approximately 98% are required for PB-TURSO to achieve cost-effectiveness at this threshold.

Budget Impact

In the CADTH base case, the budget impact is expected to be $122,345,734 in year 1, $177,817,289 in year 2, and $188,693,091 in year 3, with a three-year total of $488,856,114. The budget impact was sensitive to the assumption that PB-TURSO would not displace edaravone, and to public coverage rates. Scenario analyses tested resulted in three-year budget impact estimates ranging from $312,354,634 to $802,501,394.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: May 26, 2022

Regrets

One expert committee member did not attend.

Conflicts of Interest

None