# AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis
## Response to Public Comments on Draft Evidence Report

**August 4, 2022**

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers</td>
<td>2</td>
</tr>
<tr>
<td>Amylyx</td>
<td>2</td>
</tr>
<tr>
<td>Mitsubishi Tanabe Pharma America (MTPA)</td>
<td>6</td>
</tr>
<tr>
<td>Sanofi</td>
<td>14</td>
</tr>
<tr>
<td>Clinical Experts</td>
<td>17</td>
</tr>
<tr>
<td>Petition Letter from ALS Experts</td>
<td>17</td>
</tr>
<tr>
<td>Patient/Patient Groups</td>
<td>23</td>
</tr>
<tr>
<td>ALS Association</td>
<td>23</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
</tr>
<tr>
<td>Paul Langley</td>
<td>29</td>
</tr>
<tr>
<td>PIPC</td>
<td>32</td>
</tr>
<tr>
<td>#</td>
<td>Comment</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1.</td>
<td>Innovation in ALS treatment has been slow and riddled with failures, leaving a high unmet medical need for people living with ALS who face rapid morbidity and mortality. If approved by the FDA, AMX0035 could be the first therapy in the US indicated for the treatment of ALS that has been shown to both slow the loss of physical function and extend survival in a randomized, placebo-controlled clinical trial, either as a stand-alone therapy or when added to existing approved treatments. AMX0035 represents an important and meaningful advancement in the disease management of ALS, and after the recent approval of AMX0035 by Health Canada, we look forward to also bringing AMX0035 to US patients. Amylyx remains committed to serving the ALS community and to ensuring that people living with ALS in the US will have access to this novel medicine. In that spirit, we would like to highlight evidence on AMX0035 that should be incorporated into the revised evidence report, as well as key recommendations for changes to the methodology for your consideration.</td>
</tr>
<tr>
<td>2.</td>
<td><strong>Include recently published data on crossover adjusted survival benefit for AMX0035.</strong> While the report acknowledges the survival benefit of AMX0035, it also notes that “the method used to analyze survival is conservative as crossover from placebo to AMX0035 was not accounted for; the true survival benefit may be greater than that reported.” (page 17). A recent publication, Paganoni et al. 2022, provides an updated analysis of the interim CENTAUR and OLE survival data adjusting for treatment crossover, and suggests a greater survival benefit with AMX0035 than seen in the original ITT analysis. In this study, both intent-to-treat (ITT) and rank-preserving structural failure time model (RPSFTM) survival analyses were performed using the July 20, 2020, and most recent March 1, 2021, cutoff dates (Figure 1). Using the July 20, 2020, cutoff date, the RPSFTM analysis resulted in a difference in median survival of 10.6 months (25.8 months for AMX0035 versus 15.2 months in the group originally assigned to placebo; HR: 0.39, 95% CI: 0.17 to 0.90). We agree that the ITT survival analysis is conservative. However, we chose to not include findings from the Paganoni et al. 2022 study in our clinical review because it is difficult to account for crossover in an observational study design. The RPSFTM analysis is a post-hoc theoretical approach to examine counterfactual outcomes, and assumes immediate benefit at crossover, which was not observed in the CENTAUR trial with a 6-month follow-up, and assumes exchangeability, which is unknown and not testable. As one example, patients may not respond similarly to AMX0035 six months later into their disease. This assumption is an extrapolation of the CENTAUR trial findings to a population that would have otherwise been excluded based on enrollment criteria at the time of randomization (&lt;18 months from symptom onset).</td>
</tr>
</tbody>
</table>
0.88, \( p=0.023 \) compared with the 6.9 month difference in median survival from the ITT analysis (Figure 2). In the RPSFTM survival analysis using the March 1, 2021 cutoff date, the difference in median survival duration was 9.7 months (23.5 months for AMX0035 versus 13.8 months in the group originally assigned to placebo; HR: 0.42, 95% CI: 0.18 to 0.99, \( p=0.048 \)) compared with the 4.8 month difference in median survival from the ITT analysis (Figure 3).

We recommend that ICER include the recently published survival data that accounts for crossover effects to address the noted uncertainty in survival benefit of AMX0035. These recently published data should be reflected in the evaluation of the net health benefit rating for AMX0035.

3. **The recent data on survival benefit after crossover adjustment should be included as the base case, or at a minimum, as an additional scenario of the cost-effectiveness evaluation.**

The draft evidence report rightly acknowledges that the overall survival benefit may not match the true survival benefit. For that very reason, we believe that the recent publication using a rank preserving structural failure time model (RPSFTM) to adjust for the crossover effect on survival results provides a better estimate of AMX0035’s survival benefit. As such, we would recommend using these data in the base case of the cost-effectiveness evaluation. The RPSFTM analysis of the CENTAUR trial using the most recent March 1, 2021, cutoff date reported significant improvement in the difference in median survival (9.7 month difference after crossover adjustment [HR: 0.42, 95% CI: 0.18 to 0.99] versus 4.8 month difference from the original ITT analysis). We would suggest recalibrating the AMX0035 HR on mortality based on the RPSFTM analysis rather than based on the ITT analysis to reflect this recently published data.

The draft evidence report also includes a scenario where patients receiving AMX0035 experience no separate survival benefit to account for the uncertainty in true survival benefit. While ICER assumes that this scenario may clarify the impact of the survival benefit of AMX0035 on cost-effectiveness, it is not supported by the available evidence. Furthermore, the available evidence from the RPSFTM analysis points to the possibility that AMX0035’s
survival benefit may indeed be greater than the 4.8 months used in the base case. If ICER is not amenable to using the RPSFTM survival results (9.7 month difference after crossover adjustment [HR: 0.42, 95% CI: 0.18 to 0.99]) as a base case for the cost-effectiveness analysis, at a minimum, this is an important scenario that should be added to the current list of scenarios.

4. **Include recently published data on long-term tracheostomy/ventilation-free survival and hospitalization from the CENTAUR trial.**

In addition to the recently published survival analyses, another recent study reported on the occurrence of key events, including death, tracheostomy, permanent assisted ventilation (PAV), and first hospitalization in the CENTAUR trial and accompanying OLE. The study supports a modifying effect of AMX0035 on disease progression and demonstrates potential added benefits of AMX0035 on reducing the health burden in ALS.

The analyses in this study were focused on the modified ITT population and encompassed events occurring from the point of randomization through the July 20, 2020, cutoff date. Over the analysis period (longest post-randomization follow-up: 35 months), the risk of key events was significantly lower in patients originally randomized to AMX0035 compared with those originally randomized to placebo. Patients originally randomized to AMX0035 had a 47% lower risk of experiencing any key event compared with patients randomized to placebo (HR: 0.53, 95% CI: 0.35 to 0.81, p=0.003). The risk of death or tracheostomy/PAV were 49% lower among those receiving AMX0035 compared to placebo (HR: 0.51, 95% CI: 0.32 to 0.84, p=0.007), with median (IQR) tracheostomy/PAV-free survival duration of 25.8 (14.8-33.6) months for those initially randomized to AMX0035 versus 18.5 (11.7-not reached [NR]) months for those initially randomized to placebo. Risk of first hospitalization was also 44% lower for those originally randomized to AMX0035 compared with those randomized to placebo (HR: 0.56, 95% CI: 0.34 to 0.95, p=0.03), with median (IQR) hospitalization-free duration of NR (6.9-NR) for those randomized to AMX0035 versus 14.1 (4.2-NR) months for those randomized to placebo.

We recommend that ICER include the recent analyses of tracheostomy/ventilation-free survival and hospitalization.
to ensure completeness of the clinical evidence for AMX0035 and the data should be reflected in the evaluation of the net health benefit rating for AMX0035.

5. **Table 3.3. Overview of Amylyx and FDA results for ALSFRS-R Decline**

The analyses presented on Table 3.3 are not accurately described and some corrections are needed.

Please make the following corrections:

First row of table: FDA stated they preferred a different model in ALS (joint-rank) but did not dispute the veracity of our model. The FDA result displayed currently is not their joint-rank model (row 3 instead). Additionally, this row of the table could be misinterpreted to imply different results were derived from the same primary outcome; however, this is not the case.

Second row of table: The FDA result shown here is not a linear change from baseline result. This is the FDA’s result from a traditional MMRM. Our traditional MMRM finding was statistically significant (p=0.03) and is available in the advisory committee slides. The p-value from our linear change from baseline is listed as NR but was p=0.01 (in NEJM supplement).

Third row of table: FDA’s model did not include death equivalent (in the footnote it says joint rank was performed by ranking death and death equivalent).

6. **Table 4.7. QALY-Based Threshold Analysis Results with Health State and Standard of Care Drug Costs Included**

The results presented in this table for the threshold analyses are inconsistent with the report findings. Considering that oral edaravone + SOC was found to have a higher incremental cost-effectiveness ratio compared with AMX0035 + SOC in the base case ($11,986,000/QALY gained versus $2,136,000/QALY gained), it would be implausible for oral edaravone to have a value-based price to achieve $200K/QALY gained while AMX0035 does not.

Please update the findings in this table or provide additional language in text to address this inconsistency.
7. **Draft Questions for Deliberation and Voting**

Question number 1 suggests that the current standard of care involves concomitant treatment with both riluzole and IV edaravone.

Please revise to “riluzole and/or IV edaravone.” New question 1 should read as follows: Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of AMX0035 plus standard of care is superior to that provided by standard of care alone (i.e., multidisciplinary care that may involve treatment with riluzole and/or IV edaravone)?

We have now added “and/or” as suggested to question 1.

---

**Mitsubishi Tanabe Pharma America (MTPA)**

1. While the draft evidence report acknowledges the value of additional treatment options for amyotrophic lateral sclerosis (ALS), it has serious methodological flaws that compromise the results and incorrectly imply poor value of new treatments for ALS.

Specifically, the draft evidence report makes biased and incorrect assumptions on the efficacy and real-world use of edaravone. Further, as ICER is meant to be an independent and impartial organization, it is disconcerting that the expert panel for this report includes 2 neurologists who are known to have either a conflict of interest or previously expressed unfavorable opinions on edaravone.

We suggest that another neurologist free from any conflict be added to the expert panel. Consistent with our commitment to address unmet patient needs, MTPA submits the following recommendations to improve the accuracy of ICER’s conclusions. If the draft evidence report is left uncorrected, the final report may jeopardize access to treatment that could meaningfully impact the lives of patients and their family members affected by this devastating disease.

Regarding the implied conflict of interest, ICER staff followed up with MTPA via email and did not receive any additional information regarding a financial conflict of interest.

From the information that was provided to us, it seems that two external reviewers of the draft evidence report may have expressed a negative position towards edaravone through prior publications (specific citations or links were not provided to us) or public statements. This is not a conflict of interest. Even if intellectual conflicts of interest were being discussed, and there is little agreement on what constitutes an intellectual COI, ICER believes that no such conflict exists here. ICER’s report reviews a body of evidence, and we expect that reviewers are likely to provide input concordant with opinions they formed about that body of evidence. All external reviewers are expected to fill out our COI survey prior to their review.

The final contents of the report are authored by ICER’s staff and contracted collaborators only.
2. **Comment 1:** It is inappropriate to separate the evidence rating for the narrow population defined by the Study 19 inclusion and exclusion criteria from the rest of the oral edaravone target population.

ICER’s draft report assigned a C+ evidence rating for edaravone among patients who meet the Study 19 entry criteria and an I (insufficient) for patients who do not meet them. In contrast, the same report assigned a C++ evidence rating for AMX0035 in the general ALS population without applying the CENTAUR trial entry criteria to the assessment. This approach has serious flaws that undermine the potential value of edaravone for the 3 main reasons outlined below.

**Reason 1:** By assuming that the CENTAUR study’s efficacy findings apply to the entire labeled population for AMX0035, ICER is treating edaravone and AMX0035 inconsistently.

Both Study 19 and CENTAUR used study designs that enrich for patient populations that are expected to have measurable disease progression, so that efficacy can be determined during a 6-month trial period. If ICER limits edaravone to patients meeting the Study 19 entry criteria, then AMX0035 should be limited to patients meeting the CENTAUR entry criteria. Indeed, some of the CENTAUR entry criteria are more restrictive than those of Study 19 (e.g., confirmed diagnosis of Definite ALS, disease duration of ≤18 months). This discrepancy needs to be corrected by expanding oral edaravone beyond Study 19 entry criteria or by limiting AMX0035 to patients meeting CENTAUR entry criteria.

Including separate evidence ratings is appropriate given the evidence for an absence of benefit from RCTs in more advanced ALS populations beyond the Study 19 cohort. For edaravone we have evidence of no effect in broader populations, as opposed to AMX0035, where there is an absence of evidence in patients with more advanced ALS than those participating in the CENTAUR trial. Since we do not know if AMX0035 is similarly effective in patients with more advanced ALS than included in the CENTAUR trial, we have added this as an uncertainty to the “Uncertainties and Controversies” part in Section 3.2. If new evidence suggests AMX0035 is ineffective in different ALS populations, we would revise our report.

3. **Reason 2:** The generalizability of edaravone’s Study 19 efficacy outcomes has been demonstrated.

Several studies have demonstrated the generalizability of the Study 19 efficacy outcomes to the population that does not meet the study’s inclusion and exclusion criteria. First, a post hoc analysis of Study 16, which used a machine learning method, showed that up to 70% of patients in Study 16 would have received statistically significant benefits (Brooks et al., 2022a). Further, a post hoc analysis of the rigorous MCI-186 clinical trials program. Post hoc analyses of the RCTs or of the OLE are hypothesis generating, and do not supersede findings from high-quality clinical trials. As we noted in the report regarding Study 16, “in the group not meeting the dpEESP2y subpopulation criteria (n=131), patients...
of Study 19 analyzed outcomes of participants in a 24-week open-label extension (OLE) study who were assigned to either edaravone or placebo in the double-blinded study phase (Shefner et al., 2020). While only 15% of patients who received placebo for 24 weeks and switched to edaravone (placebo-edaravone) met the Study 19 inclusion and exclusion criteria when they rolled over to the OLE study to initiate edaravone at week 24, the functional decline observed was lower for placebo-edaravone patients at week 48 than the decline projected for those who would have remained on placebo through week 48 (−10.9 vs. −13.0, respectively) (Shefner et al., 2020). Another post hoc analysis of Study 19 reported a 33% lower loss in ALSFRS-R score loss for patients who received edaravone for 48 weeks (edaravone-edaravone patients) compared with placebo-edaravone patients (−10.26 vs. −15.20, respectively; P = 0.0038) (Brooks et al., 2022b). The decline in ALSFRS-R score observed satisfies a threshold for a clinically meaningful change; in a survey study of 65 ALS experts, 100% rated a 25% decrease in the slope of the ALSFRS-R as at least somewhat clinically meaningful (Castrillo-Viguera et al., 2010).

<table>
<thead>
<tr>
<th>4. <strong>Reason 3:</strong> Patients receiving edaravone in real-world clinical settings demonstrated its effectiveness, regardless of whether they met Study 19’s inclusion and exclusion criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>We placed more emphasis on the MCI-186 clinical trials program to determine efficacy than real-world observational studies owing to the inherent challenges and biases of who is treated and how outcomes are assessed. The study by Brooks et al. (2022c) used administrative claims data which is lacking information on key confounders and prognostic factors, including site of onset, ALSFRS-R score at baseline, and rate of progression prior to the index date.</td>
</tr>
<tr>
<td>A real-world observational study of patients with ALS in the US demonstrated the risk of death was 27% lower in the IV edaravone-treated group than the non–IV edaravone-treated, propensity matched group (HR, 0.73; 95% CI, 0.59-0.91; P = 0.005). (Brooks et al., 2022c).</td>
</tr>
<tr>
<td>Recommended solution: provide 1 clinical rating for edaravone among the general ALS population.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>Comment 2:</strong> The evidence supporting the clinical effectiveness and safety of edaravone is robust.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our rating of C+ for oral edaravone was tempered by a single small trial conducted in a homogenous population with previous negative trials; by experiences of clinical experts; and by a lack of a survival benefit during the randomized plus OLE</td>
</tr>
<tr>
<td>ICER’s draft evidence ratings for oral edaravone (C+) and AMX0035 (C++) are not supported by clinical evidence.</td>
</tr>
</tbody>
</table>
Clinical data indicate that oral edaravone’s evidence rating should be improved for the 3 main reasons outlined below.

**Reason 1:** Evidence for edaravone’s ability to slow down disease progression is robust.

In edaravone’s phase 3 pivotal study (Study 19), the LS mean difference in ALSFRS-R score change from baseline between the edaravone arm and the placebo arm was 2.49 (95% CI, 0.99-3.98; P = 0.0013) at 24 weeks (ICER, 2022). Conversely, the FDA conducted its own analysis of AMX0035 and estimated the treatment difference in change from baseline in ALSFRS-R in patients who received AMX0035 to be small and statistically insignificant (1.68, P = 0.11) (FDA, 2022). Therefore, the evidence to support IV edaravone’s ability to slow down patients’ ALS progression is stronger than the evidence for AMX0035. This is confirmed by the FDA advisory committee for AMX0035 in comments recognizing that edaravone studies demonstrated evidence for reducing functional decline (a 33% reduction) over 24 weeks of treatment, compared with placebo (FDA, 2022; p. 11).

In addition to reduction in ALSFRS-R, edaravone’s ability to slow down functional impairments in patients with ALS has been demonstrated through a variety of additional measures, such as a physical function scale (Modified Norris Scale), a quality-of-life measure (ALSAQ40), and respiratory function (forced vital capacity) and the occurrence of respiratory events (Writing Group for Study 19, 2017).

**Reason 2:** Real-world evidence supporting survival benefits of IV edaravone is available.

Survival benefits of edaravone have been demonstrated in a propensity score-matched retrospective observational analysis of patients with ALS in the US (Brooks et al., 2022c). Risk of death was reported to be 27% lower in the IV edaravone group than in the 318 non-IV edaravone-treated, propensity matched group (HR, 0.73; 95% CI, 0.59-0.91; P = 0.005) (Brooks et al., 2022c). MTPA provided this reference to ICER as supportive evidence for survival benefits of edaravone, but ICER’s draft report assumed no survival benefits among patients receiving edaravone, citing 1 observational study in Germany (Witzel et al., 2022) as support. However, the Witzel et al study should not phases with real world evidence suggesting no benefit in survival or function.

Our rating and clinical evidence review have already recognized that Study 19 provided evidence for a modest 2.5-point reduction in the ALSFRS-R score, which translated to ~33% relative slowing in decline. We also noted that secondary endpoints numerically tended to favor the intravenous edaravone group, including statistically significant improvements in the Modified Norris Scale score (an alternate ALS functional scale) and for quality of life (ALSAQ-40 score).

Study 19 only had 3 deaths during both the randomized and OLE phases. In the absence of clinical trial evidence, our estimate of no survival benefit was supported by the Witzel et al study, which provided high-quality real-world evidence. One of the main limitations of the Witzel et al study that we did not discuss in the report was the use of an as-treated study design, such that the edaravone-treated group only included patients who completed at least 4 treatment cycles. Compared to an ITT approach (completion of ≥1 treatment cycle), the Witzel at study likely yields biased estimates in favor of a treatment effect for edaravone. Also, in
overrule other evidence of edaravone’s survival benefits because the study has many important shortcomings.

First, the patients in the Witzel et al study received various formulations of edaravone, including generic formulations that may not have been prepared with the stabilizing excipients found in MTPA’s Radicava® (edaravone) injection. Because of the use of generic formulations, the results obtained in Witzel et al should not be assumed to represent effectiveness of Radicava®. In addition, in this observational study edaravone-treated patients with ALS were not matched with contemporary controls, but rather with historical controls. Additionally, only 4 covariates were used for propensity score matching, while many other models generally aim to balance groups by matching on all prognostic factors. This lack of adequate matching resulted in edaravone-treated patients progressing faster at baseline than those in the “matched” control group. Finally, Study 19 entry criteria were only met by 8% of all edaravone-treated patients.

Therefore, the repeated references to this observational study in the ICER draft report, which cannot outweigh the results of a phase 3 randomized controlled trial that was designed to evaluate safety and efficacy, are unfounded and should not be considered in the analysis of oral edaravone.

Our cost-effectiveness models, we favorably assume an indirect survival benefit for oral edaravone through its effect on slowing disease progression, even though the available evidence does not support this.

The alternate formulations of intravenous edaravone included in the Witzel et al study were all approved by Japan Medicines Agency’s generic drug approval process. If there are data to suggest different bioequivalence or clinical effectiveness, we would reconsider our inclusion of the Witzel et al study. Please note that in considering the effectiveness of oral edaravone, we also assumed equivalent effectiveness based on bioequivalence with the IV formulation.

Regarding the concern for confounding, the Witzel et al study included the most important covariates in their propensity score matching, including site of onset and ALSFRS-R score at baseline, which are not available in claims data used in the Brooks et al study (2022c). Disease progression at baseline was also similar in the edaravone-treated and the matched control group in both the overall matched cohort (p=0.11) and the EFAS subgroup that approximates the Study 19 cohort inclusion criteria (p=0.70).

We agree that where in conflict between trials and observational studies, we used findings from the RCT. Specifically, we used Study 19 to estimate the treatment effect of oral edaravone on disease progression, instead of the Witzel et al study’s estimate of no effect on ALSFRS-R.

7. **Reason 3: Edaravone has evidence for long-term product safety.**

We agree that oral edaravone has a low risk profile. However, the separate ‘I’ rating for the non-Study 19 population is warranted because in the absence of
The efficacy and safety of edaravone has been studied in a variety of clinical trials, including multiple phase 3 studies and postmarketing surveillance reviews. All safety events reported for edaravone for the first 3 years of availability in the US have been reported and analyzed in a postmarketing surveillance study, which confirmed no new safety signals beyond those already known from the previous trials (Genge et al., 2022). Further, the completed 48-week phase 3 study of oral edaravone that evaluated long-term safety and tolerability found that safety results were generally consistent with the edaravone safety profile, with no other safety concerns identified.

Recommended solution: improve oral edaravone’s combined rating.

<table>
<thead>
<tr>
<th>8. Comment 3: ICER’s base-case cost-effectiveness analysis (CEA) assumption of no efficacy benefits in 65% of patients receiving edaravone is unfounded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ICER’s draft report, the base-case CEA for edaravone assumes no efficacy benefits in 65% of the cohort entering the model. In contrast, the base-case analysis for AMX0035 assumes all patients entering the model experience the efficacy observed in the CENTAUR trial. Based on a comparison of 2 parallel CEAs using inconsistent methods, the draft report (p. 31) concludes that the cost-effectiveness of AMX0035 “is superior to that of edaravone.” When multiple treatments are compared in parallel, even qualitatively, it is critical to ensure that all comparisons are conducted consistently. If left uncorrected, this serious methodological error will compromise conclusions about the value of oral edaravone and AMX0035 for the following reasons.</td>
</tr>
<tr>
<td>Reason 1: Generalizability of edaravone’s efficacy outcomes from Study 19 and real-world clinical benefits of edaravone have been demonstrated (See Comment 1, Reasons 2 and 3).</td>
</tr>
<tr>
<td>The generalizability of edaravone’s efficacy from Study 19 has been demonstrated in a broader population of patients with ALS (Brooks et al., 2022a, Brooks et al., 2022b, Shefner et al., 2020). Further, in real-world clinical practice, patients who experience clinical benefits are more likely to initiate and continue receiving edaravone (Brooks et al., 2022c). Hence, it is incorrect to assume no efficacy among benefit, even small harms can cause net harm to patients. Also, as we noted above, the subgroup of patients in Study 16 who did not meet the dpEESP2y criteria (n=131) did numerically worse than those randomized to placebo, albeit not statistically significant (difference of -0.57 points, 95% CI: -2.55 to 1.41, p=0.57).</td>
</tr>
<tr>
<td>The rationale for limiting the efficacy of edaravone to the study 19 population is based on the results of two RCT’s that did not show an effect. No such trials exist for AMX0035. Evidence of no effect is different than a lack of evidence. We fully support the conduct of additional RCT’s to evaluate AMX0035 in broader populations.</td>
</tr>
<tr>
<td>We have changed the language in the report from, “is superior to that of edaravone,” to, “...however its cost effectiveness is numerically lower than that for edaravone. This is primarily due to the modeled prolongation in survival as observed in the CENTAUR OLE and the different standard of care treatments included in the respective clinical trials.”</td>
</tr>
</tbody>
</table>
those who do not meet the Study 19 entry criteria. As demonstrated in ICER’s scenario analysis (ICER, 2022; Scenario 5, p. E10), this assumption is an enormous driver for the incremental cost per quality-adjusted life-year gained with edaravone.

<table>
<thead>
<tr>
<th>9. <strong>Reason 2</strong>: This assumption is inconsistent with how AMX0035 was evaluated.</th>
<th>See comment above regarding a change in the wording.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reason 2</strong>: This assumption is inconsistent with how AMX0035 was evaluated.</td>
<td><strong>Reason 2</strong>: This assumption is inconsistent with how AMX0035 was evaluated.</td>
</tr>
<tr>
<td>Despite the fact that the CENTAUR inclusion and exclusion criteria were established to select a rapidly progressing population in order to demonstrate AMX0035 efficacy, ICER’s AMX0035 CEA applies the efficacy observed in the CENTAUR trial for the full cohort that enters the model. As previously noted, this use of an enrichment strategy was seen in the Study 19 and CENTAUR study designs. Therefore, if ICER limits edaravone to patients meeting the Study 19 entry criteria, then AMX0035 should be limited to patients meeting the CENTAUR entry criteria. In addition, the high discontinuation rate observed among patients receiving AMX0035 in the CENTAUR trial indicates that the efficacy data generated in the CENTAUR trial may have been skewed towards those who were responding to treatment. To estimate the cost-effectiveness of either treatment in the overall ALS population, appropriate statistical methods are required to estimate population-adjusted efficacy.</td>
<td><strong>Reason 2</strong>: This assumption is inconsistent with how AMX0035 was evaluated.</td>
</tr>
<tr>
<td>Recommended Solution: Remove the statement comparing the cost-effectiveness of oral edaravone and AMX0035. Use Scenario 5 of ICER’s draft report as the base-case analysis, where all patients who initiate edaravone will experience clinical benefits observed in its pivotal trial. Alternatively, use appropriate statistical models to impute efficacy of both oral edaravone and AMX0035 for those who did not meet the entry criteria for the respective pivotal trials.</td>
<td><strong>Reason 2</strong>: This assumption is inconsistent with how AMX0035 was evaluated.</td>
</tr>
<tr>
<td><strong>10. Comment 4</strong>: ICER’s base-case CEA should not assume survival benefits for AMX0035.</td>
<td>The evidence supporting a survival difference for AMX0035 comes from an RCT and its OLE. We are using this estimate as we feel it is the best available estimate. The rational for using this is also supported in previous comments above.</td>
</tr>
<tr>
<td>ICER’s draft CEAs assumed survival benefits for patients receiving AMX0035 but not for those receiving edaravone. Survival benefits for AMX0035 were incorporated despite the lack of conclusive evidence on its ability to prolong survival in the CENTAUR trial. In contrast, evidence of edaravone’s survival benefits is presented in a real-world</td>
<td><strong>10. Comment 4</strong>: ICER’s base-case CEA should not assume survival benefits for AMX0035.</td>
</tr>
</tbody>
</table>
11. **Comment 5:** In ICER's draft base-case CEA results, total costs for oral edaravone are disproportionately higher than AMX0035's total costs.

In the base-case CEA results, the lifetime cost of oral edaravone for a patient with ALS was estimated to be $427,000 (ICER, 2022; Table E9; p. E7), while the lifetime cost of AMX0035 was estimated to be $260,000 (ICER, 2022; Table E10; p E7) with the assumption that AMX0035 is priced the same as IV edaravone. Even with the initial 19% discontinuation rate associated with patients receiving AMX0035, this cost differential is substantial and requires further explanation. We are concerned that ICER applied the monthly discontinuation rate beyond 6 months, resulting in only ~40% of living patients in the AMX0035 arm to be on treatment at 2 years. Following this method, ~95% of edaravone patients will be on treatment at 2 years, despite the assumption of no clinical benefit to 65% of patients.

Recommended Solution: Please provide the rationale behind the substantial difference in total costs of oral edaravone and AMX0035 in respective CEAs and update the model calculations.

12. **Comment 6:** ICER’s draft CEA for edaravone makes an overly conservative assumption on how oral edaravone impacts disease progression.

ICER’s base-case CEA uses a hazard ratio estimated by the Canadian Agency for Drugs and Technologies in Health (CADTH) to apply the effect of edaravone on disease progression, which is inconsistent with CADTH recommendations on how to use this estimate. We respectfully request ICER apply the hazard ratio for transitions to all ALS health states (stages 1 to 4b) for the following reason:

CADTH’s hazard ratios are underestimated in early stages of the disease.

We chose to use the hazard ratio calculated by CADTH as it was a better parameter to measure progression compared to a relative risk based on changes to the ALSFRS-R score from the trials, which were the only other pieces of evidence we had access to. We chose to only apply the treatment effect of edaravone to stages 1-3 for several reasons: 1) in Study 16, which included a broader ALS population with more advanced disease than Study 19, edaravone did not show efficacy; 2) Study 16’s results were confirmed in Study 18 with lack of efficacy in later stages; 3) the post-hoc analysis in Study 19 specifically did not show a treatment effect in stage 4 based on the Kaplan-Meier curves. We have...
The CADTH review committee reported that the hazard ratio is underestimated in early stages of disease (stages 1-3) but overestimated in stages 4a and 4b (Common Drug Review, 2019; p. 19). For total treatment effect to be balanced, we recommend ICER to apply the ratio to all transitions to all ALS stages.

Recommended Solution: The base-case analysis should apply the delay in progression for edaravone across all health states (Stages 1 to 4b).

<table>
<thead>
<tr>
<th>Sanofi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Modelling approach based on King’s ALS clinical staging system lacks adequate precision</strong></td>
</tr>
</tbody>
</table>

ICER has developed a de novo decision analytic model consisting of six health states, including death, which tracks the severity of disease, based on the King’s ALS clinical staging system.[1]

The primary endpoint in ALS clinical trials is ALSFRS-R, as it is a widely used primary outcome measure of functional progression and severity of ALS. Per FDA Guidance, the effectiveness of an ALS treatment “should be established by the demonstration of a treatment effect (e.g., less decline, stabilization, improvement) on function in daily activities as measured, for example, by the ALS Functional Rating Scale-Revised or similar scales.”[2]

ICER highlighted that one of the reasons for choosing King’s staging system to model ALS progression was because this approach had been used in a previous submission at CADTH of edaravone for ALS. However, from an economic modeling perspective the King’s ALS clinical staging system lacks precision and is suboptimal in its ability to reflect the disease severity, as it is mainly focused on anatomical disease spread [3] in comparison to ALSFRS-R, which measures severity of functional decline in multiple domains.

We opted to use a Markov model based on the King’s staging system as it has been used previously, had data available by King’s stage for health state utilities, direct costs, indirect costs, and caregiver disutilities. The model structure was also able to accommodate available treatment effect estimates. We requested data from manufactures to allow consideration of other model structures, but no sufficient data were provided. Finally, a recent CADTH report that used a Fine til 9 based model generated results for the comparison of AMX0035 to SOC that are in line with our estimates providing cross validation of our approach.

| 2. Additionally, CADTH had pointed out several important limitations of this modelling design: [4] |

- CADTH stated that fitting a single Markov-transition matrix to longer-term progression and mortality observations in a database of ALS patients generates a significant loss of information.
- As ALS is a heterogeneous disease, CADTH noted the importance of flexibility in simulating the evolution of specific subgroups. Specifically, CADTH

See above. The data request to manufactures included requests for data on patient heterogeneity, however no such data were provided.
listed patient age, site of onset, and time in state as important predictors of disease-progression rates.

<table>
<thead>
<tr>
<th>3.</th>
<th><strong>King’s Stage converted from ALSFRS-R does not correspond well with disease severity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>To convert ALSFRS-R to King’s stages, the algorithm developed by Balendra (2014) is generally used.[5] This algorithm was used by Al-Chalabi (2020) for determining King’s stages of edaravone patients from the MCI186-19 trial and was also used in the edaravone submission to CADTH. [6]</td>
<td></td>
</tr>
<tr>
<td>The algorithm had several limitations when predicting King’s stages based on observed ALSFRS-R scores (Table 1). Firstly, the use of the algorithm led to substantial errors in classifying patients in Stage 2. Almost half of the patients were allocated to an estimated stage that was not the same as the actual stage. Secondly, Stages 4A and 4B were not studied as not enough patients were present in those stages.</td>
<td></td>
</tr>
<tr>
<td>To further evaluate how accurate the algorithm works for classifying ALSFRS-R score into King’s stage, we used a database provided by Adelphi (Adelphi ALS Disease Specific ProgrammeTM).[7] Adelphi had conducted a cross-sectional survey of neurologists and their consulting ALS patients. The data collection took place in the USA between July 2020 and March 2021. The ALS DSP sample comprised of 59 physicians and 379 patients (mean age: 59.5 years, 67% men). Physicians were requested to complete a full ALSFRS-R questionnaire for each ALS patient that consulted with them during the study period. However, most physicians did not complete the King’s staging questionnaire (only 5 patients had physician-reported King’s stage). Instead, Adelphi used Balendra’s algorithm to generate estimated King’s stages based on observed ALSFRS-R scores.</td>
<td></td>
</tr>
<tr>
<td>Figure 1 demonstrated the overlap of individual ALSFRS-R scores across King’s stages. The limited correspondence between King’s stages estimated based on the Balendra algorithm and observed ALSFRS-R scores, therefore, suggests a change in ALSFRS-R that is meaningful from a clinical standpoint does not necessarily generate a change in King’s stages and there is a risk that treatment-related</td>
<td></td>
</tr>
</tbody>
</table>

See above. An individual patient simulation model would only be possible with additional data from manufactures, which were not provided.
meaningful benefit will not be captured in economic models if using King’s Stages.

An alternative to using a King’s stages-based modelling approach would be to use an individual patient simulation model with ALSFRS-R-derived health states. An ALSFRS-R-based model would address the aforementioned methodological issues and would more accurately and precisely reflect the expected effects of disease and treatment.
1. Topic 1. Deficiencies in the evaluation of the efficacy of oral edaravone

In the report, oral edaravone received an evidence rating of C+ for patients matching the Study 19 entry criteria and I for all other ALS patients, while that of AMX0035 was higher, at C++ for all patients with ALS. We believe the C+ evidence rating of oral edaravone is unjustifiably low, and have provided several points of evidence below that support an increase in this rating.

The FDA approval of oral edaravone was based, in part, upon the evaluation of previous randomized controlled studies of intravenous (IV) edaravone, notably Study 16, Study 18, and the pivotal Study 19. Below, we discuss important context with respect to these 3 trials that we believe warrants an update to the evidence rating for edaravone.

- Study 19 was a phase 3 trial that showed significant slowing of disease progression as measured by change from baseline in ALSFRS-R score over 6 months
  - In the Study 19 primary endpoint, the LS mean difference in change from baseline ALSFRS-R was 2.49 (95% CI: 0.99 - 3.98), P = 0.0013, a 33% difference in rate of progression of ALS
  - Study 19 showed a change in baseline ALSFRS-R score for patients in the edaravone group that was greater than the change estimated for AMX0035 in an analysis conducted by an FDA advisory panel (https://www.fda.gov/media/157186/download)
  - All of the secondary endpoints in Study 19 favored edaravone, although only 2 were statistically significant in the trial (Modified Norris Scale and ALSAQ-40)
  - In its review of IV edaravone (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209176Orig1s000TOC.cfm), the FDA indicated that Study 19 was largely sufficient on its own to warrant approval of edaravone for the treatment of ALS

We agree with these findings on disease progression in Study 19. However, our rating of C+ was tempered by a single small trial conducted in a homogenous population with previous negative trials; by experiences of clinical experts; and by a lack of a survival benefit during the randomized plus OLE phases with real world evidence suggesting no benefit in survival or function.
Study 19 utilized an enrichment strategy, based on the results of Study 16, to enroll a population of patients that would have measurable disease progression, while having a good probability of survival, during the 6-month double-blind trial period (this point will be discussed in greater detail in Topic 2).

2. The ICER report states that “Studies 16 and 18 showed no benefit of edaravone on progression of ALS”; however, this does not adequately represent the clinical evidence provided by these studies, as detailed below.

- Study 16 (Abe K, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:610-617.), which included a broader population of patients than Study 19, did not meet its primary endpoint in change from baseline in ALSFRS-R score; however, all clinical trial endpoints showed the same direction of favoring edaravone.
  
  - As mentioned in the ICER report, an analysis of Study 16 found a subgroup of patients who had more homogeneous disease progression and did appear to show a significant slowing of disease progression with edaravone.
  
  - This finding was corroborated by Study 19, which used entry criteria based on that subgroup analysis of Study 16.
    - Moreover, Study 19 demonstrated long-term changes in ALSFRS-R score over 48 weeks that favored edaravone (Shefner J, et al. Muscle Nerve. 2020;61(2):218-221.).
  
  - In its review of IV edaravone, the FDA considered the subgroup analysis of Study 16 as confirmatory evidence of the efficacy of edaravone.
  
  - The generalizability of Study 19 to a broader population of patients with ALS was demonstrated in a recent study (Brooks BR, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23:49-57.), where a machine learning model was applied to Study 16 outcomes data and stratified patients based on predicted outcomes to create a novel, risk-based subgroup analysis tool. This analysis ascertained a statistically significant edaravone treatment effect in a cohort of participants with broader disease characteristics than the Study 19 inclusion criteria. Specifically, it demonstrated that up

Please refer to our responses above to the manufacturer, MTPA, which addressed comments about the need to separate evidence ratings for oral edaravone.
to 70% of patients included in Study 16 would have received statistically significant slowing of disease progression by edaravone. Therefore, we disagree with separating edaravone’s clinical evidence rating between the exact population in Study 19 and the rest of the labeled ALS population (this is addressed further under Topic 2 below).

3. • Study 18 was an exploratory trial conducted with a small population (N=25) of patients with more advanced ALS (Writing Group on Behalf of the Edaravone ALS 18 Study Group. Amyotroph Lateral Sclerosis Frontotemporal Degener. 2017;18(suppl 1):40-48.)
  o Study 18 did not meet its primary endpoint of change from baseline in ALSFRS-R score, but it was not designed to provide conclusive efficacy results and therefore should not be considered as evidence of lack of efficacy of edaravone in this patient population.
  o Moreover, it was clear from the study results that 1 outlier patient in the edaravone treatment arm experienced a decline of 31 points in the ALSFRS-R, skewing the results of the trial.
  
  Despite this outlier, Study 18 showed median values of change from baseline in ALSFRS-R score of −5.0 for edaravone vs −5.5 for placebo, indicating a modest slowing of disease progression in the edaravone group.

4. • Unwarranted use of an observational study
  o The German observational study of edaravone cited in the ICER draft report referenced the Witzel et al article (Witzel S, et al. JAMA Neurol. 2022;79:121-130.), stating that the study “found no evidence of a reduction in mortality.” However, due to the large number of significant limitations in this study, we feel it is not suitable for inclusion in the evidence report.
  o The most important limitations include the following:
    ▪ This observational study utilized a variety of formulations of edaravone, perhaps including Radicava® (edaravone) injection, but it is not clear how many patients received Radicava. Several generic formulations of edaravone were

We interpreted Study 18’s findings in the context of Study 16 showing no efficacy in the overall population, with suggestion of potential worsening in patients who did not meet what would later become the Study 19 inclusion criteria. While small in size, Study 18 corroborated these findings. We do not agree with using an unfavorable response to therapy as an appropriate reason to exclude a participant.

Please refer to our responses above to the manufacturer, MTPA, which addressed most of these same comments regarding the Witzel et al study.

Regarding the selection of control patients, there was incomplete but considerable overlap of observation time periods between the edaravone-treated patients and the matched control. The Witzel et al study included a more contemporary control group than other available observational studies, including the Brooks et al study (2022c), which chose the same index date for all controls based on when intravenous edaravone was available on the market.
utilized, many of which may have important differences in the formulation of the drug. As such, the data from the study should not be assumed to represent the efficacy of Radicava® (edaravone).

- The propensity score modeling employed by Witzel et al used only 4 covariates, whereas typical models include all prognostic factors and confounding to optimally balance the cohorts; the propensity score matching did not result in equivalent populations in the EFAS group, ie, the edaravone patients had faster disease progression at baseline than the control group.
- The Witzel et al study used historical controls that were from a larger dataset that was not contemporary with patients with ALS who had received edaravone in their study.
- Only 16 (8%) of the edaravone patients met the Study 19 criteria.
- There were deficiencies in their survival analysis; small numbers of patients and none of the KM curves reached 50% survival.
- A small observational study cannot negate results obtained in a well-conducted randomized controlled trial.

The serious limitations of this study make it inconclusive regarding the efficacy or survival benefits of Radicava® (edaravone), and the study should not be used as a basis for edaravone’s clinical rating.

In light of the above, we believe that the C+ rating for edaravone is not accurate and it is imperative to increase the evidence rating for oral edaravone to one that more accurately represents the robust data behind it.

### 5. Topic 2. Discrepancies in how oral edaravone and AMX0035 study populations were evaluated and utilized in ICER analyses

- In at least 7 places, the ICER report focuses on the topic of the study population in Study 19 in order to make the case that edaravone’s clinical benefit should be rated differently from that of AMX0035.

The rationale for including separate ratings for oral edaravone is based on available RCTs which did not find benefit in ALS populations with more advanced disease than the Study 19 population. As we noted above, the subgroup of patients randomized to edaravone in Study 16 who...
be limited to patients meeting the entry criteria of Study 19
  - The purpose of the Study 19 entry criteria was to enroll an enriched patient population that would have measurable disease progression, while having a good probability of surviving, during the 6-month double-blind trial period. This does not, however, demonstrate that edaravone has no benefit in patients who do not meet these entry criteria
  - In the FDA review of IV edaravone (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209176Orig1s000TOC.cfm), they determined that because of the heterogeneity of ALS, and in light of the clinical trial evidence for edaravone, “...it would be counterproductive to limit the indication to patients with disease severity below a particular threshold. It is not known whether there is a specific stage of disease beyond which the treatment effect wanes.”

There is no biological rationale for believing that edaravone would have an effect on disease progression only in patients who meet the Study 19 entry criteria; nevertheless, the Study 19 entry criteria were used to limit the population of patients considered to potentially benefit from edaravone in the economic analyses in the report.

did not meet Study 19 inclusion criteria did numerically worse than those randomized to placebo. Also, the pathophysiology of ALS is not well elucidated, so there is insufficient biological rationale to support extrapolating benefit given contradictory clinical trial evidence.

<table>
<thead>
<tr>
<th>6.</th>
<th>A key problem in the ICER analysis is that the same approach was not applied to AMX0035, which also utilized an enriched patient population in the CENTAUR trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>In particular, some of the entry criteria for the CENTAUR trial were more restrictive than those for Study 19, including a requirement for a diagnosis of Definite ALS according to El Escorial criteria (Study 19 allowed both Definite and Probable diagnoses) and a requirement of disease duration ≤18 months before enrollment in the CENTAUR trial (Study 19 allowed patients with ≤24 months of disease duration)</td>
</tr>
<tr>
<td>-</td>
<td>The ICER report does not mention anywhere the entry criteria for the CENTAUR trial. Discussion of the pivotal studies in the ICER report should be consistent about noting that both studies had entry criteria that selected Please see our detailed response to the manufacturer, MTPA, above. In response, we have now added this uncertainty about AMX0035’s effectiveness in populations beyond the CENTAUR trial’s inclusion criteria to our Report. We have now also moved the entry criteria for the CENTAUR trial from the Supplement to the main report in Section 3.1.</td>
</tr>
</tbody>
</table>
for an enriched population of patients with ALS

- It appears that the entry criteria for the CENTAUR trial were not used to limit the population of patients considered to potentially benefit from AMX0035 in the economic analyses in the report.
- ICER’s draft report assigned a C+ as the clinical evidence rating for edaravone among patients who meet the Study 19 criteria. However, for patients who do not meet these criteria, the draft report stated the evidence to be insufficient (I). In contrast, the same draft report assigned C++ as the clinical evidence rating for AMX0035 among the general ALS population, which does not consider that the CENTAUR study also used an enriched population of patients with ALS in their phase 2 clinical trial.

This is a serious discrepancy in how the 2 drugs were evaluated.
<table>
<thead>
<tr>
<th>#</th>
<th>Comment</th>
<th>Response/Integration</th>
</tr>
</thead>
</table>
| **Patient/Patient Groups** | **Summary**  
We strenuously object to the Draft Evidence Report’s seemingly definitive assessment of the non-cost-effectiveness oral edaravone (and by extension IV edaravone) and the methodology used to assess the cost-effectiveness of both oral edaravone and AMX0035. The methodology does not capture the value that people living with ALS, families, and society place on ALS therapies and ignores real-world data.  
Because ICER aspires to influence current and future drug-use decision making in the United States, ICER’s analyses should be based on the contemporary, real-world, American values and data – particularly when the decisions are for patients imminently facing profound disability and death. Given the complexities of the American health system, it is not appropriate to assess the burdens of ALS experienced by foreign populations, as is done in this Evidence Report. For both logical and ethical reasons, the experiences of Americans with ALS need to shape the value assessments of American drugs. Data from the United Kingdom and the Republic Korea are better suited to pricing drugs for Britons or Koreans living with ALS. The Draft Evidence Report, however, relies upon data that is a decade or more old from the United Kingdom, Korea, and the US to assess the ALS quality of life and costs.  
Furthermore, as a responsible healthcare and analytics entity, ICER should sometimes be willing to conclude that:  
- Incremental quality adjusted life years (QALYs) and equal value of life years gained (evLYG) metrics do not fully capture the patient and societal value of therapies and can be inherently discriminatory, as concluded by the National Council on Disabilities,  
- There is not sufficient pre-published contemporary, US, real-world data to build an elaborate economic model that reaches a definitive valuation for a drug, and/or  
- The patient-centered risk of a weak value assessment is too great to finalize an Evidence Report. | We completely agree that there is tremendous need for new therapies for ALS. Due to the rapid progression of the disease which may lead to severe disability or death, pricing at the high end of – or even beyond – traditional cost-effectiveness ranges might be considered. However, as of today there are still substantial remaining uncertainties about the benefits of AMX0035 and oral edaravone. As we recommend in our report, while patients and clinicians are currently waiting for more evidence to be available to support their decision-making, policymakers should debate short-term pricing options including a far lower price close to the cost of production until the benefits of the treatments can be adequately evaluated.  
We agree that QALYs do not capture the entire potential patient and societal value of therapies. This is why the QALYs are only one component of the value assessment. Please refer to the ICER Value Assessment Framework for more information. |
A reasonable approach would be ICER and stakeholders to agree on the thresholds for reaching these conclusions prior to conducting a review. That was not done in this case. Based on our own review, we find all three of these conclusions apply to this Draft Evidence Report.

2. After you review the remainder of this letter and other feedback, we request that ICER ask the voting committee the following questions:
   - Is the evidence base for costs of ALS, QALYs, and evLYG used for the Draft Evidence Report’s cost assessment sufficient to draw conclusions about the appropriateness of ALS drug pricing? Yes/No

   While major health payers currently cover IV edaravone for some ALS patients and ALS clinical trials include it as standard of care, the Draft Evidence Report’s cost-effectiveness assessment suggests that edaravone is so overpriced that health payers should never cover edaravone (IV or oral).
   - Is the evidence base and methodology of the assessment sufficient to justify Americans with ALS losing access to FDA-approved treatments like edaravone?

   When voting on the long-term value for money, the Voting Council will consider the clinical evidence (available through clinical trials, or provided to us directly by the manufacturers), results from our incremental cost-effectiveness analysis, but also other benefits, disadvantages, and contextual considerations. We believe that this is a comprehensive evidence base, which includes more metrics than just the QALYs and evLYGs that you have highlighted.

   ICER does not recommend anywhere in the report or other materials that Americans with ALS should lose access to FDA-approved treatments.

3. **Incremental QALYs and evLYG Do Not Capture Value**

   Patients, caregivers, and everyone touched by ALS agree upon its devastating physical and emotional toil – both in terms of the challenges of their lived-lives and the fear of what’s coming next. Now consider the EQ-5D-3L questionnaire, where the patient assesses the quality of their current life by checking one of three circles for each of five quality of life dimensions:

   **MOBILITY**
   - I have no problems in walking about
   - I have some problems in walking about
   - I am confined to bed

   **SELF-CARE**
   - I have no problems with self-care
   - I have some problems washing or dressing myself
   - I am unable to wash or dress myself

   **USUAL ACTIVITIES (e.g. work, study, housework, family, or leisure activities)**
   - I have no problems with performing my usual activities
   - I have some problems with performing my usual activities

   There are advantages and disadvantages to using general quality of life assessments rather than disease specific assessments. As noted above, results from CADTH using other instruments closely mirrored those in this report.

   Manufacturers (and patient groups) can develop quality of life measures and use them to evaluate new therapies. In the absence of data using alternative measures, not using cost effectiveness allows manufacturers to simply set whatever prices they wish, no matter how obviously out of line those prices are with achieved benefits.
• I am unable to perform my usual activities

**PAIN / DISCOMFORT**
• I have no pain or discomfort
• I have moderate pain or discomfort
• I have extreme pain or discomfort

**ANXIETY / DEPRESSION**
• I am not anxious or depressed
• I am moderately anxious or depressed
• I am extremely anxious or depressed

**These questions clearly do not capture the unique disabilities and devastation of the ALS experience.** Furthermore, given the progressive nature of ALS, it is not at all clear how a person living with ALS should respond to the “usual activities” dimension. Yet these are the quality-of-life questions, presented over time, commencing in 2009, to a cohort of 214 United Kingdom (UK) ALS patients – half of who were receiving lithium therapy and many of whom did not respond to quality life questions as their disease progressed – are the basis for the Evidence Report’s incremental QALY development.

Quality-of-life utilities were then assigned to the question responses using a scoring system that was developed by asking general-population UK residents questions along the lines of “what would you give to move from one health state another?” – where health states are defined by these 5 dimensions and 3 possible responses. **Neither people living with ALS nor the general population were asked questions specific to ALS**, such as “what would you give in order to not be trapped in a body that is rapidly losing muscle control?”

4. While ICER intends the parallel use of evLYG to offset the shortcomings of QALYs, it doesn’t. Compared to QALYs, evLYG, with its focus on life years, presents an even more unitary measure of patient and societal value. evLYG does not adequately measure the value of quality of life and disease therapies.

Our position aligns with the National Council on Disability (NCD), an independent federal agency making recommendations to the President and Congress. Their 2019 report “Quality-Adjusted Life Years and the Devaluation of Life with Disability” enumerates the failings

We disagree. The evLYG includes both improvements in quality of life and improvements in length of life in assessing a treatment’s value.

However, the value the evLYG assigns during periods of life extension assumes the same quality of life representative of all American adults such that the life extension occurs in a health state that is much improved compared to those who experience a debilitating disease.
of QALYs and evLYG for cost-effectiveness assessments that impact people with disabilities. They discuss several alternatives to QALYs and evLYG, including alternatives that simultaneously consider many factors relevant to healthcare value and decision-making.

By understanding a treatment’s cost per evLYG, as well as its traditional cost per QALY, policymakers can take a broader view of cost-effectiveness and be reassured that they are considering information that poses no risk of discrimination against any patient group.

5. **Cost Assumptions**

   While reliance on incremental QALYs and evLYG is a profound shortcoming of the cost-effectiveness assessment of the Draft Evidence Report, it is not the only shortcoming. In order to reach a strong cost-effectiveness conclusion, both the numerator and denominator of an assessment calculation need to be strong. Incremental QALYs and evLYG are the denominators; incremental cost is the numerator.

   In the development of medical costs, the report uses cost values from a paper that blends 2008-2011 commercial health insurance data and otherwise ignore Medicare data. Estimation of societal costs relies on a paper describing the 2013 costs of caring for ALS patients in Korea. Obviously, US medical costs and treatment protocols have changed dramatically since 2008 and there is no reason to believe that nearly 10-year-old data from Korea has any relevance.

   **High-quality, contemporary, real-world US Medicare data is available, but because ICER relies upon pre-published papers and do not conduct/sponsor primary analyses, this report ignores the data.** Unlike in the past, today most people living with ALS immediately qualify for Medicare, irrespective of age. As a result, traditional Medicare and Medicare Advantage plans provide health insurance to most ALS patients, mostly as the primary payer and sometimes as a secondary payer to the VA or employer-sponsored plans. Medicare data through 2021 is available to researchers and could be used to answer key questions such as what services do ALS patients receive, what do the services cost, how many patients receive IV edaravone, which patient receive edaravone, how long patients stay on edaravone, and how long do patients survive.

   The data we used in our model has been used previously in other analyses. We requested data on the economic impact of ALS from the manufacturers but were not provided such data. HTA bodies do not typically have the resources to conduct primary evidence generation given limited budgets and short timelines. We encourage the ALS association and/or manufacturers developing drugs to treat ALS to sponsor primary research on the economic impacts of ALS in a manner that can be used by HTA bodies to facilitate timely evaluations. We further encourage these groups to share these data.

6. **Other Considerations**

   Thank you for recommending these edits. We have revised this language in the report.
Importantly, the report also fails to adequately acknowledge the heterogeneity of ALS patients and their disease progression. For example, while more than a third of ALS patients are under age 60 and people of any age can have unmet major life goals, the report seemingly dismisses the impact of ALS patients’ ability to achieve major life goals related to education, work, or family life when it states that “for most patients, ALS occurs at an older age where many of these major life goals will not be affected.” The report also dismisses the population of ALS patients for whom edaravone has a positive effect when it says “even if edaravone is effective in the subset of patients... this population represents only 10% of all ALS patients.”

<table>
<thead>
<tr>
<th>7.</th>
<th><strong>Lack of Real-World Validity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Economic models, such as cost-effectiveness models, should have real-world validity.</strong> The real world, however, has already reached a conclusion that is contrary to the Draft Evidence Report. The report assumes that oral edaravone has the same efficacy and cost as IV edaravone and concludes that cost-effectiveness of oral edaravone far exceeds typical cost-effectiveness thresholds – with the implication being that neither IV nor oral edaravone should be covered. Yet, all major US health payers cover IV edaravone for some ALS patients. Further, it is allowed as standard of care in all ALS clinical trials, including the trials for AMX0035 used in this report, and the cost-effectiveness assessment of AMX0035.</td>
<td></td>
</tr>
<tr>
<td>The rational conclusion is that ICER’s modeling is underestimating edaravone’s value for the treatment of ALS. Further, we find that ICER’s divergent opinion is due to the failure of incremental QALYs and eVLYG to assign value that aligns with patient and societal value of therapies provided to patients who are imminently facing profound disability or death, and the report’s reliance on poor quality and irrelevant data.</td>
<td></td>
</tr>
<tr>
<td>This comment reflects a fundamental misunderstanding of cost effectiveness analysis. Coverage decisions in the US are not typically made on the basis of cost-effectiveness and drug prices in the US are not typically based on the value the drug provides. That insurers pay for edaravone provides no information about its cost effectiveness. In contrast, that many patients chose not to take IV edaravone shows that those patients concluded that the net health benefit of IV edaravone was negative.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.</th>
<th><strong>Conclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The ALS Association supports the use of high-quality data and modeling to inform decisions. Sometimes, however, the data is so limited and unreliable that the modeling does not capture the essence of the decision. In the healthcare arena, modeling using limited and unreliable data can lead to poor patient-care decisions and reputational damage for the organization promoting the model. We find the ALS</strong></td>
<td></td>
</tr>
<tr>
<td>Thank you for providing us feedback. Please refer above to all your specific questions and recommendations.</td>
<td></td>
</tr>
<tr>
<td>cost-effectiveness assessment analysis as described in the Draft Evidence Report is such a situation.</td>
<td></td>
</tr>
<tr>
<td>QALYs and evLYG do not fully capture patient and societal value, and there is simply not sufficient contemporary, US, real-world pre-published data included in this report to build an economic model that can make a credible valuation of edaravone and AMX0035. The risk to people living with ALS of a weak value assessment is too great for ICER to finalize the Draft Evidence Report.</td>
<td></td>
</tr>
<tr>
<td>Therefore, we respectfully encourage and request that ICER declines to finalize this report. Thank you in advance for your time and for your careful consideration.</td>
<td></td>
</tr>
</tbody>
</table>
1. As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment, the creation of assumption driven imaginary claims fails to meet the standards of normal science. That is, given the standards for credibility of claims, empirical evaluation, and replication, which distinguish science from pseudoscience, you persist in creating these cost-effectiveness models when it is quite clear that they have no validity. Your reports for modeled claims, many of which are produced by expert academic groups, lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of modern measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This has been detailed in a recent publication in F1000Research which has addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness. This is, by any standards of normal science, an analytical dead-end. This draft report on these two products, oral edavarone (Radicava: Mitsubishi Tanabe Pharma America, Inc) and AMX0035 (Amylyx Pharma; seeking FDA approval) in ALS, as with your previous reports, should be withdrawn.

2. The lack of understanding by CHEERS 22 and the ISPOR/ICER meme of the standards for modern measurement theory and failure to appreciate that the standard is for value claims expressed as unidimensional attributes is undeniable. Indeed the overwhelming majority of both generic and disease specific PROs produce nothing but ordinal scores. They are incapable of a robust estimate of response to therapy. CHEERS 22 and its companion textbook primer for creating imaginary value claims seem unaware of this limitation.

3. Consider the preferences (or utilities) you have applied in your assumption driven imaginary claims, including QALYs, cost per QALY claims and imaginary cost per QALY thresholds. These utilities are taken from an old report utilizing the EQ-5D-3L instrument. What the authors of this study failed to consider were: (i) the ordinal nature of multiattribute., algorithm driven preference scores (i.e., they lack invariance of comparison) and

Thank you for your continued feedback. Our Value Assessment Framework and ICER’s reference case both have been developed by consulting leading experts in the field of Health Technology Assessment and health economics. We update our framework every 3-4 years to keep it up-to-date and reflect any relevant new data or validated measures that could be used.

We welcome any additional data and evidence (including patient-reported outcomes) to be published in this, and other, disease spaces.

Thank you, your concerns are noted. As we have expressed before, we (and most health economists) are confident that changes in the EQ-5D (and other multi-attribute utility instruments) do have ratio properties. The EQ-5D value sets
(ii) whether the distribution of these scores is normal or non-normal. We know that the scores produced by the EQ-5D-3L instrument are ordinal; that is, they lack invariance of comparison and a true zero for the required ratio measurement standards. The evidence is clear cut: the algorithm is a composite equation that includes symptom responses ranked ordinally and the algorithm can produce states worse than death (or negative values). This means there is no true zero and this cannot support multiplication any more than ordinal preference scores can. I know you have denied that, arguing (as far as I could make out) that a claim for a ratio preference with a natural zero point for death (ignoring negative value scores) is entirely valid; a ratio scale in disguise. No proof has ever been provided.

4. As noted in a number of publications, the fact that the preference score is ordinal means that the QALY, multiplying time by a mean preference score, is mathematically impossible. Of course, if the scale is ordinal this means a mean value is impossible and hence the QALY is impossible. But there is a further issue: non-normality. It is assumed, typically without any evidence, that preference scores from the EQ-5D-3L/5L instruments are normally distributed with interval properties so that means and standard deviations can be estimated. However, if the distribution (for the sake of argument) is non-normal (skewed with extreme values) then estimating the standard deviation tells us nothing about asymmetry and the extreme values which may give a misleading mean value. Perhaps your expert group could tell us if the EQ-5D-3L distribution in the Jones et al paper 6 is normal or otherwise? A question that should have been addressed as a matter of good practice in all ICER evidence reports modeling imaginary claims for the various multiattribute preference scores for all disease states. Please see our responses above.

5. If the distribution is non-normal then the standard practice is to focus on the median and interquartile range; if the data are ordinal (as they are) the interquartile range is interpreted as an interval and not a distance. In the absence of a meaningful mean value the QALY is impossible. This is important because two recent applications of the EQ-5D-5L in ALS, from China and Germany, have found that the distribution of preference scores are non-normal and that the only valid distributional measures are the median and interquartile range (neither cited in the ICER report). The two studies do not report on QALYs (understandably), focusing instead of the EQ-5D-5L visual analog scale (VAS) scores which, unfortunately, are also ordinal. As Bond and Cox point out: The real problem here is that we routinely mistake the distances between fraction or percentage scores as having direct interval scale properties, when all we may really infer from the data is the ordering . Please refer to our response regarding the EQ-5D above.

Furthermore, there are advantages and disadvantages to using general quality of life assessments rather than disease specific assessments. As noted above, results from CADTH using other instruments closely mirrored those in this report.

Manufacturers (and patient groups) can develop quality of life measures and use them to evaluate new therapies. In the absence of data using alternative measures, not using cost effectiveness data are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale.
What we need to consider is relative distance; a technique to accomplish this has been applied for over 100 years in a transformation of a raw score to its natural logarithm, with a log-odds scale avoiding compression as the ends of the scale. This takes us to Rasch Measurement Theory and the creation of true bounded ratio scales to reflect the difficulty of items and the ability of respondents to realize those items (e.g., such as patient needs in ALS).

6. The result of these failures to meet the standards of normal science means that the ICER modeling should be rejected. Claims that across the board in the ALS modeling fail to be, by design, empirically evaluable; assumption driven claims on an imaginary future than can stretch for decades have nothing to recommend them. Base case results for oral edaravone plus standard of care that suggest a total cost of $598,000 with 0.93 QALYs over the assumed patients’ lifetime horizon are meaningless (Table 4.3). The base case results for AMX0035 plus standard of care at a placeholder price, with total costs of $598,000 and 1.03 QALYS are equally meaningless (Table 4.4). Extending the imaginary modeling for costs per QALY gained of $11,986,00 for oral edaravone and $2,136,00 for AMX0035 are equally misplaced (Table 4.5). Consequent assumption driven imaginary scenario claims must also be rejected (Table 4.6). As noted above, cost-per-QALY thresholds are also entirely fictitious, being built on imaginary future discounted costs and imaginary future mathematically impossible QALYs. The annual prices required to meet cost-per-QALY gained thresholds from $50,000 per QALY gained to $200,000 per QALY gained (Tables 4.7 and 4.9) are equally fanciful and under no circumstances should be considered to have any relevance whatsoever for pricing negotiations. Unfortunately, less informed media companies will take these imaginary figures at face value and promote ICER’s imaginary case for pricing adjustments.

7. Understandably, if the purpose is to put the standards of normal science and measurement theory to one side in pursuit of the mathematically impossible multiattribute QALY, then this leap of faith needs to be made clear. This is important because, as noted in previous correspondence, as claims from the past cannot support claims on the future (Hume’s problem of induction), then the door is open to a potential multitude of ALS assumption driven imaginary simulations generating competing claims; ICER is producing just one model among many. The consequences of this, facilitated by the recent CHEERS 2022 guidance for constructing assumption imaginary model simulations, is the possibility of models being created to meet the required QALY, cost-per-QALY and QALY threshold claims. A recent review in the BMJ has made clear the

©Institute for Clinical and Economic Review, 2022
existence of systematic bias in modeled QALY based cost-effectiveness claims sponsored by industry over the past 40 years that favor the sponsors product. The answer is clear cut: focus on evaluable value claims with single attribute unidimensional properties and jettison assumption driven imaginary simulations.

| 8. | While ICER clearly does not fall in this systematic bias category, the problem is one of arguments for competing (‘future realism’) assumptions and model structures. The result is that formulary committees and other health decision makers can have no faith in assumption driven model claims, even if ICER claims to have expert academic support that places it above the fray in imaginary simulated value claims. The inescapable fact is that, as noted, ICER in common with current beliefs in health technology assessment is at an analytical dead end. A framework of analysis that is removed, by design, from the standards of normal science is a claims short cut to creating approximate imaginary information for formulary decisions ; a framework that, in denying the role of hypothesis testing and the discovery of new facts as part of an ALS research program, should never have been accepted in the first place. |
| Thank you again for your continued feedback on our framework. As we mention above, our Value Assessment Framework and ICER’s reference case both have been developed by consulting leading experts in the field of Health Technology Assessment and health economics. We update our framework every 3-4 years to keep it up-to-date and reflect any relevant new data or validated measures that could be used. |

PIPC

| 1. | ICER should be weighting by severity in its models, as is becoming widely accepted by health technology assessment organizations globally. |

In recent years, many of the assumptions that cost utility analysis is built on have come under scrutiny, particularly the assumption that every unit of health gain is equal in value. Experts have noted that it is not reasonable that a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden. Several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.

Numerous economists have made the case that a system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions, and for patients who have minimal disease burden, is thought by many to be inherently unfair and skewed in the wrong direction. |

We agree that there is tremendous need for new therapies for ALS, a disease that rapidly leads to severe disability and death in many patients. Given this context, pricing at the high end of – or even beyond – traditional cost-effectiveness ranges might be considered (just as you pointed out).

However, given the substantial remaining uncertainties about the benefits of these therapies, policymakers should debate short-term pricing options including a far lower price close to the cost of production until the benefits of treatment can be adequately evaluated.
ALS is a severe condition with significant unmet need, as there are currently no effective therapies beyond symptom management. Current methodologies that factor in severity would suggest a severity multiplier of between 2-4 for a disease with this scale of relative health loss.

2. ICER continues to rely on the Quality-Adjusted Life Year, which is known to be discriminatory.  

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.

As we note above, the most recent work shows that due to diminishing returns, traditional cost utility methods, like those ICER uses, overvalue treatments for mild illnesses and undervalue treatments for highly severe illnesses, and as a result such studies recommend underpaying for treatment of severe illnesses. ICER should be evolving away from use of the QALY, and, instead, measuring value based on the most up-to-date science and improved health utilities reflecting the value to the patient.

3. Caregiver burden must be fully incorporated into ICER’s model.

Caregiver burden in ALS is profound. As the disease progresses, there is greater need for informal and paid caregiving. Among 600 caregivers participating in the ALS Focus Caregiver Survey, 68% reported spending more than 30 hours per week providing care and nearly half felt unprepared for changes in caregiving responsibilities as ALS progressed. The majority of caregivers also report a marked decline in their own physical and mental health as the patient’s condition progresses. We agree there is a need to incorporate caregiver burden. We added a caregiver QoL scenario from the modified societal perspective. We assumed 1 caregiver per patient, who had a mean age equal to the patient. To estimate the caregiver’s lifetime, we applied the US background mortality rate. The model was extended to incorporate the caregiver’s lifetime time horizon. We used King’s stage-specific utility estimates from the literature to estimate the caregiver’s lifetime utility. We used bereavement disutility from a study of caregivers to terminally ill cancer patients as we could
As such, the societal perspective is a more relevant choice than the health care perspective in the case of ALS. NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for diseases such as Alzheimer’s, Multiple Sclerosis, and Parkinson’s disease. It is also the recommended perspective for cost-effectiveness models of the second panel on cost-effectiveness and ISPOR.

4. ICER should include estimates of the “option value” of successful treatment for interventions slowing progressive diseases with high mortality rates, like ALS.

Innovation in medicine does not happen in a vacuum. The traditional approach to cost-utility analysis used by ICER in this report measures the value of a health innovation by comparing benefits to costs assuming no further improvements in medical technology in the future. In real terms this overlooks the fact that life-extending, or progression-delaying innovations can allow patients to live until the next breakthrough, or stay in less severe disease states longer. Other than the obvious benefits of such an outcome, there is also the tangential benefit that these patients could ultimately access improvements in medical technology in the near future. These benefits that would not have accrued to them, if they hadn’t benefit from current innovations, or “option value” of a health innovation should be factored into the model. As long as medical technology continues to advance, there will be option value in extended survival, or innovations that delay progression. Failing to account for this value ignores a potentially important source of benefit to patients, especially in areas of rapid innovation.

We disagree with further inclusion of “option value” in our base case findings. Option value is a concept that is difficult to quantify given uncertainties about future drug development and is therefore not routinely included in value assessments. In addition for option value to be fully included, we would need to include not only the future possible intervention’s health gains but also the future possible intervention’s costs. These costs are often left out of “option value” demonstration projects making them biased estimates of value (Li et al 2022, Lee et al 2022).

5. ICER should be placing a greater emphasis on distributive effects of new therapies.

Rather than concentrating only on the net cost-effectiveness for a hypothetical archetypal patient, ICER should be considering the impact new treatment options may have on the ALS population writ large.

Distributive effects in cost-effectiveness analyses and corresponding value-based treatment prices can have unintended consequences including leading to policy decisions within subgroups that are not substantiated by evidence. Distributive effects are important for understanding the comparative clinical effectiveness of new therapies; however, therapies are generally not priced based on such distributive effects but are priced at the population level. Therefore, the cost-effectiveness analysis findings focus on this same population-level context.

One challenge ALS patients face is access to specialized multidisciplinary ALS clinics, which is considered standard of care for the treatment of ALS. There are over 200 ALS clinics in the U.S., but these clinics are not geographically distributed. Several states have only one or two clinics. This is a large driver of intervention-generated inequality in...
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>ICER’s model structure does not appropriately represent a progressive disease, like ALS. ICER’s model structure does not appropriately represent a progressive disease, like ALS. The model structure oversimplifies ALS, and relies too much on categorization, which likely underweights the value of small changes in the rate of progression. A better choice for comparing therapy to standard of care would be a time-to-event methodology, such as a discrete event simulation model (DES), or a discretely integrated condition event (DICE) model, looking at changes in ALS Functional Rating Scale (ALSFRS-R).&lt;br&gt;&lt;br&gt;ALS is a highly heterogeneous disease, and a known limitation of the Markov model is that it is only appropriate when the disease in question is largely homogenous. Patients, caregivers, and clinical experts emphasized to ICER the need for multiple different mechanisms of action because ALS is a heterogeneous illness with multiple molecular pathways leading to neuronal death. It is well established that generating and reporting of differential value assessment across subgroups in heterogeneous diseases leads to substantial health gains, both through treatment selection and coverage. PIPC would advise ICER to move away from the assumption that all patients are the same, and the value to each can be determined by the estimation of a single point average, and move to producing ranges that are more representative of heterogeneous patient populations. <strong>The progressive nature of ALS was an important consideration in the development of the model and has been directly included within the model structure with the use of the King’s ALS clinical staging system. The King’s staging system was selected for this model for several reasons including its wide use in the clinical community and its ability to accommodate non-sequential jumps in health states which depict realistic clinical scenarios.</strong>&lt;br&gt;&lt;br&gt;While we, and the clinical and patient experts we engaged with, recognize that there is a heterogeneous rate of disease progression and treatment effect across disease stages among patients with ALS, the data to inform these analyses are not available to incorporate in the analysis. ICER follows a transparent and collaborative process that welcomes stakeholders to engage in model comparison exercises with our team. We are not aware of a patient-level model in ALS to allow for this comparison; however, our inputs and assumptions are transparently detailed in our draft Evidence Report and could be used by external teams in replicate models with different structural assumptions. It is unclear if a patient-level simulation would yield different findings compared to our cohort-level approach; however, we welcome these insights from the community.</td>
</tr>
<tr>
<td>7.</td>
<td>An ALS-specific patient-reported outcome tool should be used in ICER’s model, as research has shown that the EQ-5D is insensitive to health gain in the ALS population. An ALS-specific patient-reported outcome tool should be used in ICER’s model, as research has shown that the EQ-5D is insensitive to health gain in the ALS population. A recent study highlighted how limited the EQ-5D is as a measure of quality of life in ALS patients. It showed that There are advantages and disadvantages to using general quality of life assessments rather than disease specific assessments. As noted above, results from CADTH using other instruments closely mirrored those in this report.</td>
</tr>
</tbody>
</table>
there is a considerable lack of content validity and convergent validity for generic patient-reported outcome tools (PROs) in domains highlighted as important for ALS patients. It also showed that the correlation between generic PROs and disease specific ALS PROs was low. It concluded “generic PROs [such as EQ5D] covered only half of the domains important to individuals with ALS suggesting the need for an ALS specific preference-based measure to better reflect the health-related quality of life of this population.”

Manufacturers (and patient groups) can develop quality of life measures and use them to evaluate new therapies. In the absence of data using alternative measures, not using cost effectiveness allows manufacturers to simply set whatever prices they wish, no matter how obviously out of line those prices are with achieved benefits.

References
