July 13, 2022

Public Comments
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Re: **AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis (ALS)**
Draft Evidence Report

Dear ICER Team:

On behalf of the patients and families we serve, we appreciate the opportunity to comment on the Draft Evidence Report for a cost-effectiveness assessment of AMX0035 and oral edaravone.

Summary

The ALS Association is committed to ensuring that all people with ALS are provided immediate, full coverage and affordable access to new therapies and that payors use methodologies that value the lives of all people with ALS. **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,[1]

- 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.

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.

After you review the remainder of this letter and other feedback, we request that ICER ask the voting committee the following questions:

1. 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

2. 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?

Background

The ALS Association works with ALS community members, stakeholders, and government policymakers to ensure coverage decisions reflect the urgent and unmet need for therapies for all people living with ALS. We reach this end by adhering to a core set of values ensuring:

- All people with ALS are provided immediate, full coverage and affordable access to new therapies;
- Payors use methodologies that appropriately value and respect the lives of all people with ALS;
- Health care utilization techniques and other administrative barriers that delay or decrease access to drugs for people with ALS and other neurodegenerative diseases are prohibited; and
- The use of arbitrary, discriminatory value assessments that limit access to ALS drugs, such as the use of metrics like Quality Adjusted Life Year (QALY) or the Equal Value Life Years Gained (evLYG) are prohibited.

ALS is a rare, progressive, debilitating, heterogenous, and inevitably deadly disease. Most patients die within a couple of years of symptom onset.[2] Before people with ALS die, they will lose most muscle function and will be dependent on people and technology for every aspect of daily life – a life that many persons with ALS continue to enjoy and value. Patients may also

experience various medical complications resulting from their paralysis and immobility, such as pressure ulcers or pneumonia, which require acute medical treatment.

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: [3]

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
- ◯ 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.[4,5]

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?*"

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 of QALYs and evLYG for cost-effectiveness assessments that impact people with disabilities.[6] They discuss several alternatives to QALYs and evLYG, including alternatives that simultaneously consider many factors relevant to healthcare value and decision-making.[7]

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.[8] 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.

Other Considerations

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[9] 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*."[10] 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*."[11]

Lack of Real-World Validity

Economic models, such as cost-effectiveness models, should have real-world validity. 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.[12] Further, it is allowed as standard of care in all ALS clinical trials, including the trials for AMX0035 used in this report,[13] and the cost-effectiveness assessment of AMX0035.[14]

The rational conclusion is that ICER's modeling is understating 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.

Conclusion

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 cost-effectiveness assessment analysis as described in the Draft Evidence Report is such a situation.

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.

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.

Sincerely,

Neil Thakur, Ph.D.
Chief Mission Officer
The ALS Association

[1] National Council on Disability, "Quality-Adjusted Life Years and the Devaluation of Life with Disability", 2019.
[2] Chio, et al, "Prognostic factors in ALS: A critical review", 2009.
[3] EuroQOL, "EQ-5D | Samples / Demonstration versions", UK English EQ-5D-3L. Note: at the time of the study EQ-5D-5L was just being introduced as an upgrade to EQ-5D; EQ-5D was renamed to EQ-5D-3L.
[4] Jones, et al, "Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis", including supplement, 2014.
[5] UKMND-LiCALS Study Group, "Lithium in patients with amyotrophic lateral sclerosis (LiCALS): a phase 3 multicentre, randomised, double-blind, placebo-controlled trial", 2013.
[6] National Council on Disability, "Quality-Adjusted Life Years and the Devaluation of Life with Disability", 2019.
[7] Ibid, page 63.
[8] Oh, et al, "Socioeconomic costs of amyotrophic lateral sclerosis according to staging system", 2015. The Oh paper was relied upon within the Thakore paper, citation 72 of ALS Draft Evidence Report.
[9] CDC, MMWR, Prevalence of Amyotrophic Lateral Sclerosis - United States, 2012–2013, 2016.
[10] ICER, ALS Draft Evidence Report, 2022, Page 33.
[11] ICER, ALS Draft Evidence Report, 2022, Page 18.
[12] As of July 12, 2022, coverage is provided by Medicare, United Health Care, Aetna, Cigna, and various (and perhaps all) Blue Cross and Blue Shield Plans (eg, Premera).
[13] ClinicalTrials.gov, HEALEY ALS Platform Trial – Master Protocol, accessed July 12, 2022.
[14] ICER, ALS Draft Evidence Report, 2022, Page 6.