February 24, 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 Background and Scope**

Dear ICER Team,

On behalf of people living with ALS, their families and the ALS Association we appreciate the opportunity to comment on your Draft Background and Scope Document (Draft Scoping Document) for a cost-effectiveness evaluation of AMX0035 and oral edaravone.

We have several requests for revisions to the Draft Scoping Document.

1. **We ask that your primary analysis include the value of all ALS patient care, both medical and supportive, including the value of unpaid caregiving.**
2. **We ask that the Scoping Document define how you will measure quality of life and assign patients to health states, as well as document that the measure and the assignments align with ALS patients' self-assignments of their quality of life and health.**
3. **We also request that you make some specific, focused changes to the Scoping Document**.

We discuss each request in greater detail below.

Background

The ALS Association works with the ALS community members, stakeholders, and government policymakers to ensure pricing and 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 value principles assuring:

- All people with ALS are provided immediate, full coverage and affordable access to new therapies;
- Payors use methodologies that value the lives of all people with ALS;
- Health care utilization techniques and/or 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.

As you state, ALS is a rare, progressive, debilitating, heterogenous, and deadly disease. Before the patient dies, he or she will lose most muscle function and will be dependent on people and technology for every aspect of daily life – a life that many ALS patients continue to have the cognitive ability to enjoy and value. The person with ALS also may experience various medical complications resulting from their paralysis and immobility, such as pressure ulcers or pneumonia, that require acute medical treatment.

Loss of muscle function and dependency are expensive. Depending on disease subtype and stage, as well as the patient's directives, home, and family support system, the patient will require extensive supportive care, including: paid and unpaid caregivers, mobility assistance, transportation assistance, home modification, mechanical ventilation, enteral nutrition, adaptive equipment and supplies, long-term care facility care, and hospice care.

At an advanced disease stage, patients require care twenty-four hours a day, seven days a week, sometimes by two caregivers. According to Genworth, a long-term care insurer, the 2021 medium cost for a home health aide was $27 per hour or $19,710 per month of 24-hour care.[1] While data show the total cost of caregivers and supportive care for those with ALS can easily exceed $10,000 per month, current documentation of this data is insufficient in capturing the true cost challenges associated with supportive care.[2,3]

These supportive costs are the direct result of ALS disease. Yet, you propose that your cost-effectiveness analysis will primarily focus on "direct medical care costs" and, data permitting, will consider "productivity impacts and other indirect costs" in a separate, secondary analysis (page 6 of the Draft Scoping Document).

Requests

1. We ask that your primary analysis include the value of all ALS patient care, both medical and supportive, including the value of unpaid caregiving. We firmly believe that all caregiving has value, including care provided by family members – care that often removes family members from paid employment.

We strongly object to you dividing the cost of care for ALS patients between medical and non-medical and including only medical care costs in your primary cost-effectiveness analysis. We also object to the apparent assertion that only medical costs are "direct" costs of the disease. We note that you do not define what constitutes a "medical care cost" and assume that your definition does not include the full array of medical and supportive care. For example, we suspect you do not intend to include all the costs of enteral feeding within your primary analysis. Enteral feeding costs include:

- Insertion of the gastrostomy tube;
- Gastrostomy tube supplies;
- Medical and nutritional supervision;
- Enteral nutrition; and
- Enteral feeding and non-medical supervision, often by family members.

While the last bullet is generally considered "non-medical," it is costly and absolutely essential. None of the other health care services or supplies listed above are effective if the patient is not actually fed. Similar examples can be provided for other medical and supportive care including but not limited to speech, swallowing and mobility challenges. People living with ALS also require paid and unpaid support for activities for daily living including personal hygiene, dressing, toileting, transferring or ambulating, and eating.

Relegating a portion of the costs of caring for an ALS patient to secondary status, and even possibly ignoring the costs due to lack of data, is improper from both a societal and a health insurer (payer) perspective. The above supportive care costs are real and direct costs of ALS. With the exception of unpaid caregiving, these costs are often paid for by health insurance plans, particularly Medicare, Medicaid, and Veterans Affairs (VA) plans – the payers for nearly all ALS patients who have progressed to the stage where they need supportive care. Medicaid

and VA plans pay family members to provide supportive care, thereby converting them from unpaid to paid status.

Furthermore, a lack of quality supportive care very often moves care into the more expensive acute care and medical facility settings. The patient who is not well cared for at home by unpaid caregivers is more likely to end up in a hospital with pressure ulcers or pneumonia. A patient with ALS who does not have a supportive family will ultimately need to have care in a long-term acute care facility.

A successful ALS treatment will extend lives, improve quality of lives, and reduce acute and supportive care costs. All cost savings should be included in a cost-benefit analysis of the treatment – irrespective of whether the costs are arbitrarily classified as medical or non-medical.

2. We ask that the Scoping Document define how you will measure quality of life and assign patients to health states, as well as document that the measure and the assignments align with ALS patients' self-assignments of their quality of life and health.

While we recognize that quality adjusted life years (QALYs) as the primary outcome and equal value life years gained (evLYGs) are integral to your cost-effectiveness analysis framework, we wish to record our objection to the use of QALYs as the primary outcome and evLYGs as an alternative outcome for the cost-effectiveness analysis. Neither measure captures the value of life from the perspective of a patient disabled by ALS. Of particular importance to people living with ALS is the ability to maintain level of function for as long as possible and to slow the progression of the disease.

QALYs are inherently discriminatory against people with disabilities, as their lives are assigned a lower quality score and are therefore implicitly deemed less worthy of being extended. We strongly endorse the positions and findings within the National Council on Disability's 2019 Report to the President, "Quality-Adjusted Life Years and the Devaluation of Life with Disability".[4]

Furthermore, while we appreciate that you have tried to address objections to QALYs by introducing evLYGs, evLYGs, by virtue of being quality-neutral, do not address the quality of life that is highly valued by ALS patients. If you use QALYs, a major gap in the Scope of Comparative Value Analyses section of the Draft Scoping Document (page 6) is that you do not define how you will measure quality of life and assign patients to declining "health states".

We suspect you will rely, at least in part, on mapping the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) measurements to quality of life. In our experience, however, ALSFRS-R's 48-point scale, which was developed as a tool to assess functional status and the disease progression in ALS patients, is an ineffective method for describing ALS quality of life. For example, while patients highly value their ability to communicate with loved ones and caregivers, including with assistive technology, communication is dwarfed by physical function measures within ALSFRS-R and does not consider assistive technologies. As noted by Goldstein and colleagues twenty years ago, "*Quality of life (QOL) in patients with ALS does not correlate with physical function. Unfortunately, many quality of life (QOL) instruments which have been used to assess individuals with ALS are heavily weighted toward strength and physical function, and therefore fail to capture other important non-health related factors*."[5]

We are also concerned with the possibility of people without ALS assessing the quality of ALS patients' lives. In our experience, the utility assigned to an ALS patient's life is much lower when the assessment is made by people without ALS.

3. Finally, we also request that you make the following specific, focused changes to the Scoping Document.

- Strengthen the first paragraph (page 1) to include a more comprehensive list of the supportive care often required by ALS patients.
- Restate the ALS gender ratio (page 1, paragraph 3). The assertion that males are twice as likely to develop sporadic ALS as females is inaccurate. The average gender difference is a factor of about 1.3 – higher at younger ages and lower at older ages.[6]
- Call out the increased relative risk of ALS incidence among veterans and consider veterans as a potential subgroup.[7]

*****

We look forward to reviewing the Revised Scoping Document.

Sincerely,

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

---

[1] https://www.genworth.com/aging-and-you/finances/cost-of-care.html
[2]Nonoyama, et al, "Healthcare utilisation and costs of home mechanical ventilation", Thorax, 2018, doi:10.1136/thoraxjnl-2017-211138.
[3] Schönfelder, et al, "Costs of illness in amyotrophic lateral sclerosis (ALS): a cross-sectional survey in Germany", Orphanet Journal of Rare Diseases, 2020, doi:10.1186/s13023-020-01413-9
[4] https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[5] Goldstein, Atkins, and Leigh, "Correlates of Quality of Life in people with motor neuron disease (MND)", Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, doi: 10.1080/146608202760834120.
[6] McCombe and Henderson, "Effects of Gender in Amyotrophic Lateral Sclerosis", Gender Medicine, 2010, doi:10.1016/j.genm.2010.11.010.
[7] McKay, Smith, Smertinaite, et al, "Military service and related risk factors for amyotrophic lateral sclerosis", Acta Neurologica Scandinavica, 2020, doi: 10.1111/ane.13345.

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

February 24th, 2022

Since Amylyx was founded in 2013, we have been working tirelessly to bring a new, effective treatment option to the ALS community. We believe that AMX0035 is an important and meaningful addition to the disease management of ALS and remain steadfast in our commitment to ensuring that people living with ALS will have access to this novel medicine, if approved.

As ICER embarks on this review, we would like to raise four critical points we hope are considered, not only in the scoping document, but also during the entire evaluation.

1. **The high unmet need of people living with ALS and the need for approved treatment options should always be kept front and center during the evaluation process.**

ALS is a universally progressive, ultimately fatal, neurodegenerative disease marked by the rapid loss of motor function due to the degeneration of motor neurons in the central nervous system.[1,2,3] People affected by ALS eventually require assistance with activities of daily living, ultimately experiencing respiratory compromise, complete paralysis, and death due to respiratory failure.[4,5,6] Median survival is reported to be between 20 to 50 months from symptom onset; 80% of people with ALS die within 2-5 years of diagnosis.[7,8]

Despite currently available treatments, there remains a high unmet medical need for people living with ALS who face rapid morbidity and mortality.[9,10,11,12] ALS is historically a notoriously difficult area for drug development due to its rapid progression and rare disease status. Decades of therapeutic trials have resulted in almost universal failure to show differences in function or survival. AMX0035 represents a meaningful advance in treatment by demonstrating both improved functional and survival outcomes in a randomized, controlled trial.

Although there are currently two approved products for ALS in the U.S., riluzole (Rilutek™) and edaravone (Radicava™), the disease remains rapidly progressive and fatal.

2. **The clinical trial populations of AMX0035 and IV edaravone are materially different and unsuitable for indirect treatment comparisons.**

The study population in the randomized controlled trial (RCT) phase of CENTAUR[13] is fundamentally different than that included in the edaravone ALS RCTs. The CENTAUR trial was conducted exclusively in the U.S. at Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) multidisciplinary centers, while all 3 RCTs for edaravone were conducted exclusively at Japanese sites where specialized, multidisciplinary ALS clinics were yet to become standard clinical practice.[14] This can introduce differences between the studies in the underlying standard of care that cannot be adjusted statistically.

Edaravone studies also classified participants with ALS using the Japanese ALS Severity classification scale, which is not used elsewhere.[15,16] Further, there were additional eligibility criteria for the edaravone studies that were not required for CENTAUR: that the change in ALSFRS-R score over the pre-baseline observation period was between -1 and -4 and, in Study 19, that each patient had a score of at least 2 on every item of the ALSFRS-R. These differences in eligibility criteria resulted in significant differences in disease severity between the populations included in AMX0035 and edaravone studies. For instance, the baseline ALSFRS-R was 6.2 points lower for the AMX0035 arm in CENTAUR compared to the edaravone arm in Study 19. All these differences in trial inclusion criteria, coupled with the fact that the trial populations were from different geographical regions receiving different standards of care and had significantly different disease severity at baseline, render an indirect treatment comparison that is methodologically inappropriate.

3. AMX0035 is the first therapy to demonstrate in a placebo-controlled setting statistically significant benefits on function and survival in people with ALS, and these benefits were achieved on top of background use of riluzole and/or edaravone.

AMX0035 has been evaluated in a single, two-phase, clinical study (CENTAUR) conducted across 25 NEALS centers in the U.S. from June 2017 to March 2021.[17,18,19] The first part of the study, the RCT phase, was a 24-week, randomized, double-blind, placebo-controlled study designed to evaluate the effects of AMX0035 on preservation of function as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R), upper and lower limb muscle strength as measured by the Accurate Test of Limb Isometric Strength (ATLIS), and respiratory function as measured by slow vital capacity (SVC) (percent of predicted normal), and survival.[20,21] The second phase of CENTAUR was an open-label extension (OLE) to evaluate the long-term safety and efficacy of AMX0035 in participants with ALS who had completed the 24-week RCT phase on the study drug.[22,23] AMX0035 demonstrated a statistically significant advantage compared with placebo in delaying functional disability as well as improving overall survival in participants with ALS. Efficacy analyses from the CENTAUR trial demonstrated the following:

- Statistically significant differences observed on the primary outcome: the ALSFRS-R rates of decline at 24 weeks favored AMX0035-treated participants versus participants who received placebo (p=0.03). Participants treated with AMX0035 had 34% longer retention in function compared to placebo. These results were supported by multiple sensitivity analyses that included subgroup analyses for approved concomitant ALS medications.
- Statistically significant differences were maintained at 48 weeks for participants started on AMX0035 in the randomized phase vs those started on placebo in the randomized phase then switched to AMX0035 in the open-label phase over 48 weeks, as measured by the ALSFRS-R total score (p=0.02; 4.23-point difference in favor of AMX0035, i.e., more retention of function), upper limb strength as measured by the ATLIS Upper score (p=0.03), and respiratory function as measured by SVC (p=0.04). ATLIS total score approached a significant difference for the group originally randomized to AMX0035 (p=0.05).
- Up to 3 years after study randomization, participants originally randomized to AMX0035 had longer median survival compared to those originally randomized to placebo. The original

AMX0035 group had a 44% lower risk of death compared to the original placebo group over long-term follow-up (p=0.02).

- Consistent effects based on the hazard ratio were seen when looking at time to death only, time to death or permanent ventilation, time to hospitalization, death or ventilation supporting the consistency and robustness of the effect.
- Sensitivity analyses including covariates for use of concomitant medications were concordant (p<0.05) suggesting a consistent treatment effect from AMX0035 on survival whether participants received riluzole, edaravone or both.

4. A 2-point difference on the ALSFRS-R is clinically meaningful.

The ALSFRS-R is a well-validated measure of clinical function that is highly correlated with clinical progression and survival in people with ALS and shows strong internal consistency and construct validity.[24] A 2-point difference in the ALSFRS-R may represent the difference between being able to ambulate with some difficulties versus no ability to walk, or between eating successfully with some difficulty and needing a feeding tube (see Figure 1).[25,26,27] As each domain only includes five levels from 0 (cannot do) to 4 (normal), the prevention of 1 unit of worsening in a single domain has been deemed meaningful and desirable for people living with ALS.[28] Further, a survey of US ALS clinicians and clinical researchers demonstrated that the majority of those surveyed believe that a therapy that resulted in a change of 20% or greater in the slope of the ALSFRS-R would be clinically meaningful. The CENTAUR trial exceeded this result.[29]

Thank you for the opportunity to offer our views on the draft scoping document for AMX0035 and oral edaravone for the treatment of ALS.

Sincerely,

Machelle Manuel

S. Machelle Manuel, PhD
Vice President and Head of Global Medical Affairs
Amylyx Pharmaceuticals

Appendix

	4	3	2	1	0
Speech	Normal speech	Detectable speech disturbance	Intelligible with repeating	Speech + nonvocal communication	Loss of useful speech
Walking	Normal walking	Early walking difficulties	Walk with assistance	Nonambulatory functional movement	No purposeful leg movement
Dressing	Normal function	Independent, but with effort or less efficiency	Intermittent assistance needed	Attendant needed for self-care	Total reliance on others for self-care
Swallowing	Normal eating	Early problems; occasional choking	Dietary consistency changes	Supplemental tube feedings needed	Only enteral or parenteral feeding

Figure 1. A 2-point difference could be a significant enough motor ability difference to cause the following functional changes: being able to speak intelligibly with some repeating versus no verbal communication, having mildly impaired walking versus being unable to walk, being able to dress with effort versus requiring an attendant, having some swallowing difficulties versus needing a feeding tube.[30]

References

[1] Arthur KC, Calvo A, Price TR, Geiger JT, Chio A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun. 2016;7:12408.
[2] Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017;377(2):162-172.
[3] Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27(10):1918-1929.
[4] *Op. cit.* Brown RH, et al. 2017.
[5] *Op. cit.* Masori P, et al. 2020.
[6] Shoesmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. CMAJ. 2020;192(46):E1453-E1468.
[7] ALS Society of Canada. What is ALS? https://www.als.ca/what-is-als/about-als/. Published 2018. Accessed June 29, 2021.
[8] Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019;32(5):771-776.
[9] *Op cit.* Arthur KC, et al. 2016.
[10] *Op cit.* Brown RH, et al. 2017.
[11] *Op. cit.* Masori P, et al. 2020.
[12] NeuroVERSE. IMPACT ALS - Investigation and Measuring Patient and Caregiver Trends About ALS, Harvard Dataverse, V2. https://doi.org/10.7910/DVN/HG3MYW. Published 2019. Accessed July 03, 2021.
[13] Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. N Engl J Med. 2020; 383:919-930.
[14] Canadian Agency for Drugs and Technologies in Health. Edaravone (RADICAVA): Pharmacoeconomic Review Report. 2019.

[15] Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):610-617.
[16] Writing Group, Edaravone ALSSG. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512.
[17] Amylyx Pharmaceuticals Inc. *AMX0035: Clinical Study Report [Data on file].* 2021.
[18] Paganoni S, Hendrix S, Dickson SP, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle Nerve.* 2021;63(1):31-39.
[19] *Op. cit.* Paganoni S, et al. 2020.
[20] *Op. cit.* Amylyx Pharmaceuticals Inc. 2021.
[21] *Op. cit.* Paganoni S, et al. 2020.
[22] *Op. cit.* Amylyx Pharmaceuticals Inc. 2021.
[23] *Op. cit.* Paganoni S, et al. 2021.
[24] Cedarbaum J, Stambler N, Malat E, et. al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. Journal of the Neurological Sciences. 1999;169:13–21.
[25] *Op. cit.* Amylyx Pharmaceuticals Inc. 2021.
[26] *Op. cit.* Paganoni S, et al. 2020.
[27] *Op. cit.* Cedarbaum J, et al. 1999.
[28] Op. cit. Cedarbaum J, et al. 1999.
[29] Castrillo-Viguera C, Grasso D, Simpson E, et. al., Clinical significance in the decline of ALSFRS-R. Amyotrophic Lateral Sclerosis. 2021;11:178-180.
[30] Op. cit. Cedarbaum J, et al. 1999.

February 24, 2022

Biogen welcomes the opportunity to comment on ICER's assessment of therapies for Amyotrophic Lateral Sclerosis (ALS) including AMX0035 and oral edaravone. Biogen is a pioneer in neuroscience with a robust pipeline of therapies for both genetic and broad ALS. Like other neurodegenerative diseases, ALS is devastating and impacts not only diagnosed patients, but also pre-symptomatic genetic carriers, families, caregivers, and society. There are limited therapeutic options available today despite significant research efforts to identify disease-modifying treatments for ALS, as there have been more than 50 failed clinical trials since 1993[1,2] and only two approved therapies. To that end, we support the development of holistic frameworks that foster innovation, encapsulate the full value of innovative therapies, and preserve the decision-making between the patient and healthcare provider.

Patients diagnosed with ALS have a median survival of 3-5 years after symptom onset[3], with only 10% of patients surviving more than 10 years[4,5]. Median time from symptom onset to diagnosis ranges from 9.5 months to 2.5 years[6,7,8]. Given the rapid progression of disease and challenges in diagnosis, it is important to remove as many barriers as possible to detect and treat ALS.

We appreciate ICER's efforts to incorporate elements important to all stakeholders and will highlight a few important considerations in the draft scoping document including:

1. **Considerations for a clinical evidence review and comparative framework**
2. **Considerations for the development of a value framework**
3. **Considerations on health inequities and paving the pathway for change in ALS treatment**

Considerations for a clinical evidence review and development of a comparative framework

There are many challenges in conducting a clinical evidence review and creating a comparative framework for ALS therapies. These challenges include, but are not limited to, heterogeneity of the disease and trial baseline characteristics, as well as limitations and issues of sensitivity with endpoints used in both clinical trials and practice.

Age of onset, location of onset, progression of symptoms and motor neuron involvement introduce heterogeneity and can impact the rate of progression[9]. Heterogeneity may also exist in the rate of progression between those with and without genetic mutations, as well as between sub-types of genetic mutations. Many genetic mutations (e.g., C9orf72, SOD1, etc.) can be associated with shorter survival and/or faster decline[10].

Additionally, functional decline in ALS in general, like other neurodegenerative disorders, has been shown to occur in a non-linear fashion, which may lead to inaccurate statistical assumptions and have negative implications for the testing of investigational therapies in clinical trials[11]. Moreover, based on guidance from regulators[12], different clinical trials may have utilized different enrichment strategies which could contribute to a higher level of heterogeneity between trials, creating challenges in comparison.

The ALS Functional Rating Scale-Revised (ALSFRS-R) is inexpensive and easy to access and complete via patient self-report or by a proxy/caregiver or clinician (including through telemedicine assessments). Although it is validated in the broad ALS population, there are

challenges and limitations when using this tool to assess treatment efficacy in the context of a heterogeneous disease state.

It is an ordinal, questionnaire-based rating scale, composed of 12 questions which assesses 4 functional domains, for a total score of 0 to 48[13]. Two patients with ALS may have identical total scores on the ALSFRS-R but differ substantially in terms of their stage of disease or overall prognosis[14,15]. Subjectivity of the scale and inconsistent standardization for administration can lead to large intra-subject variability—with sudden increases of 5 points or more observed commonly across 2 consecutive visits[16]. In addition, questions on the ALSFRS-R are not evenly weighted, such that a loss of certain points may reflect a minor or a major decline in function, depending on the specific question or subdomain[13,17]. Non-linear decline of the ALSFRS-R, particularly early and late in disease, reduces its predictive value[11]. Further, floor and ceiling effects have been recognized, leading to poor discrimination on certain items for more severely disabled patients and mildly disabled patients, respectively[18]. Finally, in a survey of 103 ALS patients and caregivers, nearly half of the respondents indicated concerns that parts of the ALSFRS-R do not accurately reflect patients' abilities[19].

Recommendation: Heterogeneity of disease course and baseline characteristics within trials, as well as limitations of endpoints, must be adjusted for during development of a comparative framework. Further, consider using multiple endpoints, including biomarkers and patient reported outcomes, in the creation of a framework and evaluation of its limitations.

Consideration for the development of a value framework

In the development of a value framework, it is critical to incorporate the considerations and challenges of a comparative clinical framework. Moreover, consideration of aspects relevant to patients, as well as the limitations of current economic models, need to be addressed.

With respect to the perspective of the value framework, Biogen commends ICER for considering additional benefits and disadvantages. We urge ICER to incorporate these considerations in the base case of the final value framework.

With respect to endpoints important to patients, it has been demonstrated that, while the ALSFRS-R is a widely used tool, it does not incorporate many aspects of disease that may be important to patients[19]. These include aspects such as depression[20,21], anxiety[21], fatigue and reduced exercise capacity[22,23], muscle stiffness[3], muscle cramps[3], and pain[24].

It is also important to understand limitations with current economic models and the implications of using them to inform value frameworks and potential recommendations. Currently, some economic models have used the King's ALS staging system. Both The King's classification criteria and the Milano-Torino (MiTos) staging system are derived from select questions of the ALSFRS-R, thus perpetuating the limitations of the ALSFRS-R itself.

There are, however, challenges with using a classification system based off the ALSFRS-R that go beyond the limitations of the instrument itself. While they do provide classification necessary for the development of a Markov based model, the King's staging system is substantially more sensitive in the early stages[25] and can lead to value framework results which do not fully capture the value of treatment value for patients in more advanced stages.

More generally, within a cost-effectiveness framework, modestly effective life-prolonging treatments of refractory chronic progressive disabling (and eventually fatal) diseases such as ALS

are particularly disadvantaged because of the large cost burden imposed by background care from prolonged survival[26]. There are also situations when effective treatments are not cost-effective even if applied at zero cost, as discussed in a National Institute of Health and Care Excellence methods article[27]. The use of QALYs, both to calculate the cost-effectiveness of ALS drugs and treatments and its significant role in this report as value arbiter, discriminates against ALS patients and their families. Recent research advancements propose methods to reduce the inequitable effects of the QALY and better reflect societal preference for investment in health technologies, which address the most severe diseases, like ALS[28].

Recommendation: Develop a de novo economic model with a societal perspective, utilizing multiple endpoints or criteria, which does not discriminate against those in early (or more advanced) stages of the disease, and incorporates the broadest perspective of value.

Considerations on health inequities and paving the pathway for change in ALS treatment

ALS therapies hold the promise of transforming the lives of people living with a debilitating and terminal disease. We recognize that our impact derives not only from our focus on researching and developing innovative therapies, but also from our commitment to helping patients access and benefit from our medicines. For ALS patients in the United States, there are existing health and healthcare disparities that have the potential to influence utilization patterns, access to treatment, and may ultimately negatively impact patient outcomes. It is the shared responsibility of all healthcare stakeholders, including Biogen, to find solutions that facilitate the continuity of care throughout the patient journey, and reduce economic and geographic barriers to access.

Understanding the high unmet need for disease-modifying therapies in ALS, investigators are increasingly looking to disease biomarkers as a potential means of overcoming the challenges and difficulties of relying solely on traditional functional or clinical outcome measures, such as the ALSFRS-R. One such biomarker with prognostic and pharmacodynamic utility in ALS is neurofilament. It has been recently shown that serum neurofilament light chain (NfL) has prognostic value in ALS, and that levels remain relatively stable over time[29]. Baseline NfL levels may aid prediction of future ALSFRS-R slope decline and survival, and thus imbalances in baseline NfL can confound assessment of treatment effect[30]. Change in NfL levels following a therapeutic intervention may provide pharmacodynamic evidence of a treatment effect[30]. A goal for the near-term future, is that the increasing understanding and utility of biomarkers in clinical research, and clinical care, will ultimately help support the appropriate and quicker use and access to ALS treatments.

Recommendation: It is imperative that any framework and recommendation be mindful of disparities in healthcare and promote access to care, and encourage investment into innovative therapies and trial design to advance care for patients with ALS.

Biogen appreciates the opportunity to provide comment to the draft scoping document for ICER's assessment of therapies for Amyotrophic Lateral Sclerosis (ALS) including AMX0035 and oral edaravone. We do encourage ICER to consider all aspects of this analysis and ensure that these recommendations are accounted for during the development of ICER's framework.

References

1. Petrov D, Mansfield C, Moussy A, Hermine O. ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment? Front Aging Neurosci. 2017 Mar 22;9:68. doi: 10.3389/fnagi.2017.00068. PMID: 28382000; PMCID: PMC5360725.
2. Mitsumoto H, Brooks BR, Silani V. Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved? Lancet Neurol. 2014 Nov;13(11):1127-1138. doi: 10.1016/S1474-4422(14)70129-2. PMID: 25316019.
3. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med. 2017;377(2):162-172.
4. ALS Association. Who gets ALS? http://www.alsa.org/about-als/facts-you-should-know.html. Accessed March 22, 2021.
5. National Institute of Neurological Disorders and Stroke. Amyotrophic lateral sclerosis (ALS) fact sheet. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet. Accessed March 22, 2021.
6. Galvin M, Ryan P, Maguire S, et al. The path to specialist multidisciplinary care in amyotrophic lateral sclerosis: a population-based study of consultations, interventions and costs. PloS One. 2017;12(6):e0179796.
7. Nzwalo H, de Abreu D, Swash M, Pinto S, de Carvalho M. Delayed diagnosis in ALS: the problem continues. J Neurol Sci. 2014;343(1-2):173-175.
8. Williams JR, Fitzhenry D, Grant L, Martyn D, Kerr DA. Diagnosis pathway for patients with amyotrophic lateral sclerosis: retrospective analysis of the US Medicare longitudinal claims database. BMC Neurol. 2013;13:160.
9. Bendotti C, Bonetto V, Pupillo E, et al. Focus on the heterogeneity of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21(7-8):485-495. Doi 10.1080/21678421.2020.1779298.
10. Cammack, AJ, Atassi N, Hyman T et al. Prospective natural history study of the C9orf72 ALS clinical characteristics and biomarkers. Neurology. 2019;93(17):E1605-1617. doi 10.1212/WNL.0000000000008359
11. Gordon PH, Cheng B, Salachas F, et al. Progression in ALS is not linear but is curvilinear. J Neurol. 2010;257(10):1713-1717. doi:10.1007/s00415-010-5609-1
12. Food and Drug Administration (FDA). Amyotrophic lateral sclerosis: developing drugs for treatment. Guidance for industry. 2019. https://www.fda. gov/drugs/guidance-compliance-regulatory-information/guidances-drugs. Accessed 16 Feb 2022.
13. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169(1-2):13-21. doi:10.1016/s0022-510x(99)00210-5
14. Franchignoni F, Mora G, Giordano A, Volanti P, Chiò A. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry. 2013;84(12):1340-1345. doi:10.1136/jnnp-2012-304701

15. Franchignoni F, Mandrioli J, Giordano A, Ferro S; ERRALS Group. A further Rasch study confirms that ALSFRS-R does not conform to fundamental measurement requirements. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(5-6):331-337. doi:10.3109/21678421.2015.1026829
16. Bakers JNE, de Jongh AD, Bunte TM, et al. Using the ALSFRS-R in multicentre clinical trials for amyotrophic lateral sclerosis: potential limitations in current standard operating procedures. Amyotroph Lateral Scler Frontotemporal Degener 2021:1-8.
17. Fournier CN, Bedlack R, Quinn C, et al. Development and Validation of the Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS). JAMA Neurol. 2020;77(4):480-488. doi:10.1001/jamaneurol.2019.4490.
18. Bacci ED, Staniewska D, Coyne KS, et al. Item response theory analysis of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised in the Pooled Resource Open-Access ALS Clinical Trials Database. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(3-4):157-167. doi:10.3109/21678421.2015.1095930.
19. Boyce D, Robinson M, Collet M et al. An assessment of the ALSFRS-R by the ALS community: A mixed methods study. Presented at 32nd International Symposium on ALS/MND2021; December 7-10; (Virtual).
20. Roos E, Marlosa D, Ingre C et al. Depression in amyotrophic lateral sclerosis. Neurology. 2016;86(24):2271-2277.
21. Carvalho T, Sanguinett de Almeida LM, Araujo Lorega CM, et al. Depression and anxiety in individuals with amyotrophic lateral sclerosis: a systematic review. Trends Psychiatry Psychother. 2016;38(1):1-5.
22. Stambler N, Charatan M, Cedarbaum JM; ALS CNTF Treatment Study Group. Prognostic indicators of survival in ALS. Neurology. 1998;50(1):66-72.
23. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. Lancet. 2011;377(9769):942-955.
24. Handy C, Krudy C, Boulis N Federici T. Pain in Amyotrophic Lateral Sclerosis: A Neglected Aspect of Disease. Neurology Research International. 2011. Article ID 403808, 8 pages.
25. Fang T, Al Khleifat A, Stahl DR, et al. Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener.2017:18(3-4):227-232.
26. Thakore NJ, Pioro EP, Udeh BL, Lapin BR, Katzan IL. A Cost-Effectiveness Framework for Amyotrophic Lateral Sclerosis, Applied to Riluzole. Value Health. 2020 Dec;23(12):1543-1551. doi: 10.1016/j.jval.2020.06.012. Epub 2020 Oct 9. PMID: 33248509
27. Davis S. Assessing Technologies That Are Not Cost-Effective at a Zero Price [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Jul. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310371/
28. Lakdawalla DN, Phelps CE. Health Technology Assessment With Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach. Value Health. 2021 Feb;24(2):244-249. doi: 10.1016/j.jval.2020.10.003.
29. Lu CH, Macdonald-Wallis C, Gray E, et al. Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis [published correction appears in Neurology.

2015 Sep 8;85(10):921]. Neurology. 2015;84(22):2247-2257. doi:10.1212/WNL.0000000000001642

30. Benatar M, Zhang L, Wang L, et al. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. Neurology. 2020;95(1):e59-e69. doi:10.1212/WNL.0000000000009559

February 25, 2022

Comments Related to ICER ALS Scoping Draft

We lost Mom to ALS in 1997 and I have been an involved advocate since. Thank you for the opportunity to comment on your draft.

Costs and Disease Burden

These surveys seem to miss a lot of expenses such as cost of having things done at home because caregivers have no time. Other examples are the cost of buying and running the gas-guzzling accessible van, the expense of prepared meals, therapy for the kids, lost educational opportunities for the kids, employment loss or scaling back, career implications for the caregiver, etc. As Mom would say, these things are not chopped liver.

Cognitive Involvement, FTD

At the 2021 ALS MND Symposium, a presentation indicated that 50% of people with ALS have some kind of cognitive involvement. It is on a spectrum that has 10% at the end with full FTD.

Prevalence in the US

You quote CDC data that are misleading. Those 16,500 are only the cases that they found. A 2017 paper showed that the CDC registry found only 57% of ALS cases when compared to some more complete urban studies. ALSA alone says that they serve 20,000 people with ALS in a year. Given the incidence cited, 16,500 just doesn't pass a reasonableness test. Also, there are around 7,000 death certs annually in the CDC Wonder database with a G12.2 MND code as the underlying cause of death. I think that 25,000-30,000 is a much more reasonable estimate of the US ALS population at any moment. Unfortunately they die quickly and those faces are constantly changing.

Oral Radicava

When Treeway was working on oral edaravone, they did a study that showed that their oral product had superior bioavailability to the infusion product. Is it possible that oral edaravone will not only be more convenient but also be a better therapeutic?

Will it be possible for people using the infusion product today to switch to the oral form if they are not able to swallow? Can the oral product be crushed to be mixed in soft food or used in a feeding tube?

Rate of Decline

I do not understand this sentence in the draft --
"There was consensus among clinical experts that a two-to-three-point reduction on the ALSFRS-R scale constituted a modest benefit."

What is the period of time referenced? And is this a reduction from the expected trajectory?

One of the challenges I've seen in people who are in trials is that they try to figure out if they are getting worse less quickly than they were getting worse before. That's a difficult thing to measure, especially when the ALS decline isn't linear.

To me, every person with ALS has a slope of decline. The therapy that reduces that slope in any degree has value. If the slope gets flat, that is astronomically valuable. Even a modest reduction in the decline is helpful to someone with ALS and the family. Sometimes even a slight reduction in the decline is the bright spot people might need to find technologies and supportive care that will help them lead even more meaningful and purposeful lives.

There is another reference in the draft to populations that are fast progressors versus slow progressors. How is that measured?

Standard of Care

Thank you for mentioning ALS multidisciplinary care as the standard of care, but we must not ignore the fact that there are many people who do not have access to clinics today. That standard of care is wonderful, but it is not available to many because of locations, economics, family situations, or caregiving requirements. This is a diversity-equity-inclusion issue, and we should not assume that everyone has access to that standard of care.

For some with ALS who do not have access to multidisciplinary care, a drug intervention may be their only shot at slowing the disease down, even a little.

Contextual Considerations List

ALS is a permanent disability. We need to remember that interventions can make life more productive and more meaningful, even when on a permanent disability.

We hope that there is a respect that for someone with ALS, major life goals after dx may be different than before dx. The post-dx goals are every bit as important and as valuable (if not more) than the healthy person may have had.

Caregivers often will not speak to family life implications of ALS because they don't want to sound like they are complaining. ALS impact on caregivers is profound and touches every aspect of life. ALS impact on caregiver health should also be considered. This is a side-effect of ALS that may not show up until after the person with ALS has died.

Lifetime

"Lifetime" is a tough concept for those with ALS. They are on the ALS clock, yet they also have every right to have the best lifetime we can provide to them.

Few people living with ALS today will even be around in five years. The 25,000-30,000 faces of ALS change constantly. ALS has a relatively high incidence and a low prevalence. That's a toxic combination, and it makes it difficult to do apples/apples comparisons with other diseases. "Five years" isn't a concept that fits ALS well.

Mitsubishi Tanabe Pharma America, Inc.
525 Washington Blvd., Suite 400
Jersey City, NJ 07310
TEL 908-607-3010 FAX 201-610-1293

RE: MTPA's Response to ICER's Draft Scoping Document on AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis (ALS)

February 24, 2022

Dear Dr. Pearson:

On behalf of Mitsubishi Tanabe Pharma America (MTPA), the manufacturer of an investigational oral formulation of edaravone and intravenous (IV) edaravone (RADICAVA®), we are submitting this letter during the Public Comment Period. Our aim is to provide important context and information for consideration in your refinement of the Draft Scoping Document. The IV formulation of edaravone was approved by the FDA in May 2017 based on clinical trial data showing significantly less functional decline in symptoms of ALS with edaravone compared with placebo. Edaravone's efficacy, safety profile, and tolerability have been established in MTPA's rigorous development program that includes multiple clinical trials, post hoc analyses, and post-marketing observational studies with patients with ALS (Yoshino and Kimura, 2006, Writing Group on Behalf of the Edaravone ALS 19 Study Group, 2017a, Writing Group on Behalf of the Edaravone ALS 19 Study Group, 2017b, Jackson et al., 2019, Shefner et al., 2020; Al-Chalabi et al., 2021; Brooks et al., 2022; Genge et al., under review; Brooks et al., under review).

Comment 1: ICER's comparative effectiveness analysis for oral edaravone should account for the availability of long-term data for edaravone based on post hoc analyses of the pivotal trial and post marketing surveillance studies for IV edaravone

As demonstrated in published bioequivalence and pharmacokinetic studies of the oral suspension and IV formulations of edaravone (two manuscripts by Shimizu et al., 2021), the composition and dose of the 105-mg edaravone oral suspension provides equivalent plasma exposure to that of the IV dosing regimen of 60-mg edaravone for the treatment of ALS. As stated on Page 3 of the Draft Scoping Document, the evidence for oral edaravone will have to rely on data generated for IV edaravone. We recommend ICER incorporate in the comparative effectiveness assessment safety and efficacy data from not only the randomized controlled trials but also post hoc analyses of those trials and longer-term surveillance data for the IV formulation of edaravone (Jackson et al., 2019; Shefner et al., 2020; Al-Chalabi et al., 2021; Brooks et al., 2022; Genge et al., under review; Brooks et al., under review). In addition, to ensure ICER considers between-study-differences in incorporating outcomes from different studies, we recommend ICER review published systematic review and meta-analyses of edaravone's safety and efficacy outcomes (Luo et al., 2019).

Comment 2: Comprehensive outcomes measures should be included in the comparative effectiveness, cost effectiveness analyses, and contextual considerations to fully measure the benefits of treatments for ALS

On page 4 of the Draft Scoping Document, in addition to the listed outcomes, we recommend ICER consider comprehensive outcomes that measure life limitations in patients with ALS such as the need for using wheelchairs, canes, artificial nutrition, feeding tubes, speech generative devices, and hospice. As noted in ICER's Draft Scoping Document, for patients and caregivers, "maintaining

mobility and the ability to perform routine activities are what matter most to people with ALS." In an analysis of US administrative claims conducted among ALS diagnosed patients who received IV edaravone, the average time for progression to walking aids, artificial nutrition, ventilation, invasive ventilation / speech generating devices and hospice were estimated to be 16 to 21 months (Hagan et al., 2021). This may be compared with an analysis from a similar set of historical controls, who progressed more rapidly in these milestones (Meng et al., 2018).

Comment 3: ICER's clinical and economic analyses should leverage real-world evidence data from observations of patients who received IV edaravone

In addition to the results from randomized controlled trials demonstrating that IV edaravone slowed loss of physical function (e.g., Writing Group on Behalf of the Edaravone ALS 19 Study Group, 2017b), we recommend that ICER incorporates real-world evidence demonstrating long-term effectiveness of edaravone. ICER's Draft Scoping Document (page 2) states that riluzole is the only approved drug that is believed to prolong survival. We recommend ICER to update this statement as new data supporting the potential effect of edaravone in prolonging survival are becoming available. For instance, the overall survival benefit of patients with ALS treated with IV edaravone for at least 12 months, compared with a control group was investigated in a retrospective, observational, propensity score–matched cohort study using an administrative claims database (Brooks et al., under review).

Comment 4: If approved, oral edaravone will offer benefits that cannot be captured in standard clinical effectiveness rating methodology and cost-effectiveness analyses. These benefits must be considered carefully in ICER's assessment

1. Need for treatment based on risk of death or progression to permanent disability, magnitude of the lifetime impact on individual patients of the condition being treated

   ALS is a fatal neurodegenerative disease with rapid progression of symptoms (Mehta et al., 2018; Miller et al., 2009a; Salameh et al., 2015). Most patients with ALS will need assistance with activities of daily living, with subsequent progression leading to respiratory compromise and eventual respiratory failure, which is a leading cause of death in ALS (Kiernan et al., 2011). Therefore, the need for new treatment options is clear, where the consequences of the disease progression on patients and their caregiver are devastating. Oral edaravone provides another treatment option for slowing disease progression in patients with ALS.

2. Patients' ability to manage and sustain treatment regimen despite complexities, while providing patients and caregivers greater flexibility with an oral formulation to participate in education, work, or family life

   Having the oral option to receive edaravone may reduce burdens from patients and their caregivers such as frequently traveling to infusion centers or hospitals and taking time away from family, work, and education. ICER's Draft Scoping Document notes treatment burden and costs as "major factors in whether [patients] would try new therapies with modest benefits" and "clinicians generally believed an oral formulation of edaravone would be used by more patients." Having an

option to receive treatment in the comfort of their own home is valuable to many patients and their family members.

3. Potential to help address health inequality

   Having an additional oral treatment option will likely promote health equality by providing more flexibility for patients with ALS to treatment access, dosing and its potential benefits

4. Other factors: Value of innovation

   Despite the typical ALS prognosis that involves rapid progression to life-limiting conditions and death, the treatment options for ALS are limited. Importantly, edaravone was the first treatment approved for reducing the loss of physical function in ALS. While the exact mechanism of action is unknown, edaravone is an innovative therapy that has an impact on many of the pathological processes involved in ALS, including oxidative stress (Guo, Z, et al 2020), endoplasmic reticulum stress (Fan, J, et al. 2013; Qi, X, et al. 2004; Srinivasan, K, et al. 2012), and mitochondrial dysfunction (Takayasu, Y, et al. 2007). In addition to the unique mechanism of action, oral edaravone provides patients with flexibility in their choice of method of administration.

Comment 5: ICER's cost-effectiveness analysis report should include an analysis from the societal perspective (by incorporating indirect costs) as a co-base case analysis

ALS affects patients and their family members mentally, physically, and economically. Hence, the societal costs of care are substantial relative to direct health care costs. For example, a 2012 analysis of costs of ALS estimated that over 20% ($14,682 / $63,848) of the total annual costs per person in the US were due to indirect costs (The Lewin Group, 2012). Indirect costs for patients and their family members can be significant in this population even before the patients require intensive assistance for selfcare because of their frequent healthcare appointments and IV infusions. The impact of caregiving on family members' quality-of-life has been discussed widely in this population. We recommend ICER identify and apply disutility of ALS on caregivers in the cost-effectiveness model.

****

We appreciate the opportunity to engage with ICER and look forward to a continued dialogue for the review of treatments for ALS. If you have any questions, please contact me at Gustavo_Suarez@mt-pharma-us.com.

Sincerely,

Gustavo Suarez, MD
Vice President, Medical Affairs
Mitsubishi Tanabe Pharma America, Inc.
525 Washington Blvd. Ste 2620
Jersey City, NJ 07310
Gustavo_Suarez@mt-pharma-us.com

References

Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Dec;15(7-8):610-7.

Al-Chalabi A, Chiò A, Merrill C, Oster G, Bornheimer R, Agnese W, Apple S. Clinical Staging in Amyotrophic Lateral Sclerosis: Analysis of Edaravone Study 19. J Neurol Neurosurg Psychiatry. 2021 Feb;92(2):165-171.

Brooks BR, Berry JD, Ciepielewska M, Liu Y, Zambrano GS, Zhang J, Hagan M. Intravenous Edaravone Treatment in Amyotrophic Lateral Sclerosis Is Associated With Improved Survival: Results From an Administrative Claims Analysis. Manuscript in preparation for submission.

Brooks BR, Heiman-Patterson T, Wiedau-Pazos M, Liu S, Zhang J, Apple S. Edaravone Efficacy in Amyotrophic Lateral Sclerosis With Reduced Forced Vital Capacity: Post-hoc Analysis of Study 19 (MCI186-19). Under review in PLOS One.

Brooks BR, Pioro EP, Katz J, Takahashi F, Takei K, Zhang J, Apple S. Slowing the loss of physical function in amyotrophic lateral sclerosis with edaravone: Post hoc analysis of ALSFRS-R item scores in pivotal study MCI186-19. Muscle Nerve. 2022 Feb;65(2):180-186.

Fan J, Long H, Li Y, Liu Y, Zhou W, Li Q, et al. Edaravone protects against glutamate-induced PERK/EIF2alpha/ATF4 integrated stress response and activation of caspase-12. Brain Res. 2013;1519:1-8.

Genge A, Brooks BR, Oskarsson B, Kalin A, Ji M, Apple S, Bower L. Analysis of the US Safety Data for Edaravone From the Third Year After Launch. Under review in Drugs in R&D.

Guo Z, Wu HT, Li XX, Yu Y, Gu RZ, Lan R, et al. Edaravone protects rat astrocytes from oxidative or neurotoxic inflammatory insults by restoring Akt/Bcl-2/Caspase-3 signaling axis. IBRO Rep. 2020;8:122-8.

Hagan M, Harrison A, Ciepielewska M, Zhang J, Liu Y, Apple S, Time to Event Milestones in Patients With Amyotrophic Lateral Sclerosis Treated With IV Edaravone: Results From a US Administrative Claims Analysis, Presented at the American Academy of Neurology/AAN 2021 Virtual Annual Meeting | April 17–22, 2021.

Ito H, Wate R, Zhang J, Ohnishi S, Kaneko S, Ito H, et al. Treatment with edaravone, initiated at symptom onset, slows motor decline and decreases SOD1 deposition in ALS mice. Exp Neurol. 2008 Oct;213(2):448-55.

Jackson C, Heiman-Patterson T, Kittrell P, Baranovsky T, McAnanama G, Bower L, Agnese W, Martin M. Radicava (edaravone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. Amyotroph Lateral Scler Frontotemporal Degener. 2019 Nov;20(7-8):605-610. doi: 10.1080/21678421.2019.1645858.

Kalin A, Medina-Paraiso E, Ishizaki K, Kim A, Zhang Y, Saita T, et al. A safety analysis of edaravone (MCI-186) during the first six cycles (24 weeks) of amyotrophic lateral sclerosis (ALS) therapy from the double-blind period in three randomized, placebo-controlled studies. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(suppl 1):71-9.

Luo L, Song Z, Li X, Huiwang, Zeng Y, Qinwang, et al. Efficacy and safety of edaravone in treatment of amyotrophic lateral sclerosis—a systematic review and meta-analysis. Neurol Sci. 2019 Feb;40(2):235-41.

Mehta P, Kaye W, Raymond J, Punjani R, Larson T, Cohen J, et al. Prevalence of amyotrophic lateral sclerosis - United States, 2015. MMWR Morb Mortal Wkly Rep. 2018 Nov;67(46):1285-9.

Meng L, Bian A, Jordan S, et al. Profile of medical care costs in patients with amyotrophic lateral sclerosis in the Medicare programme and under commercial insurance. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(1-2):134-142.

Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009a Oct 13;73(15):1218-26.

Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009b Oct 13;73(15):1227-33.

Qi X, Okuma Y, Hosoi T, Nomura Y. Edaravone protects against hypoxia/ischemia-induced endoplasmic reticulum dysfunction. J Pharmacol Exp Ther. 2004;311(1):388-93.

Salameh JS, Brown RH, Jr., Berry JD. Amyotrophic lateral sclerosis: review. Semin Neurol. 2015 Aug;35(4):469-76.

Shefner J, Heiman-Patterson T, Pioro EP, Wiedau-Pazos M, Liu S, Zhang J, Agnese W, Apple S. Long-term edaravone efficacy in amyotrophic lateral sclerosis: Post-hoc analyses of Study 19 (MCI186-19). Muscle Nerve. 2020 Feb;61(2):218-221.

Shimizu H, Nishimura Y, Shiide Y, Matsuda H, Akimoto M, Matsuda M et al. Evaluation of Pharmacokinetics, Safety, and Drug-Drug Interactions of an Oral Suspension of Edaravone in Healthy Adults. Clin Pharmacol Drug Dev. 2021;10(10):1174-1187.

Shimizu H, Nishimura Y, Shiide Y, Yoshida K, Hirai M, Matsuda M, Nakamaru Y, Kato Y, Kondo K. Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adult Subjects. Clin Pharmacol Drug Dev. 2021 Oct;10(10):1188-1197. doi: 10.1002/cpdd.952.

Srinivasan K, Sharma SS. Edaravone offers neuroprotection in a diabetic stroke model via inhibition of endoplasmic reticulum stress. Basic Clin Pharmacol Toxicol. 2012;110(2):133-40.

Takahashi F, Takei K, Tsuda K, Palumbo J. Post-hoc analysis of MCI186-17, the extension study to MCI186-16, the confirmatory double-blind, parallel-group, placebo-controlled study of edaravone in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(suppl 1):32-9.

Takayasu Y, Nakaki J, Kawasaki T, Koda K, Ago Y, Baba A, et al. Edaravone, a radical scavenger, inhibits mitochondrial permeability transition pore in rat brain. J Pharmacol Sci. 2007;103(4):434-7.

The Lewin Group. Cost of amyotrophic lateral sclerosis, muscular dystrophy, and spinal muscular atrophy in the United States. March 1, 2012. Available at: https://www.mda.org/sites/default/files/Cost_Illness_Report.pdf. Accessed August 9, 2016.

Writing Group on Behalf of the Edaravone ALS 16 Study Group. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(suppl 1):11-9.

Writing Group on Behalf of the Edaravone ALS 17 Study Group. Exploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(suppl 1):20-31.

Writing Group on Behalf of the Edaravone ALS 18 Study Group. Exploratory double-blind, parallel-group, placebo-controlled study of edaravone (MCI-186) in amyotrophic lateral sclerosis (Japan ALS severity classification: grade 3, requiring assistance for eating, excretion or ambulation). Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(suppl 1):40-8.

Writing Group on Behalf of the Edaravone ALS 19 Study Group. Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017a Oct;18(suppl 1):55-63.

Writing Group on Behalf of the Edaravone ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017b Jul;16(7):505-12.

Yoshino H, Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (phase II study). Amyotroph Lateral Scler. 2006 Dec;7(4):241-5.

Inspired by patients.
Driven by science.

February 24, 2022

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted electronically at: publiccomments@icer-review.org

Re: Request for Public Input on ICER's Draft Background and Scope Document, "AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis"

To Whom It May Concern,

UCB is a global biopharmaceutical company with nearly 8,500 employees globally, inspired by patients and driven by science. As an innovator company, UCB annually reinvests a quarter of its revenue back into research and development, and is working to develop novel therapies for Amyotrophic Lateral Sclerosis (ALS) as part of the HEALY ALS Platform Trial. As such, UCB welcomes the opportunity to provide feedback on ICER's assessment of new ALS treatments. Overall, we are aligned with ICER's general framework for evaluating ALS as outlined by the population, interventions, comparators, and outcomes of interest. Below we offer more detailed feedback on ICER's proposed methodology, in the hope of improving the ALS assessment framework for existing and developing treatments, for ICER's consideration:

a. UCB strongly recommends that ICER reconsider a.) the structural limitations of precedent QALY-based frameworks, and b.) the relevance of existing cost-effectiveness thresholds in situations where a treatment regimen is less cost-effective, not due to the cost of the drug itself, but rather, the high costs associated with prolonged survival, which is the nature of ALS treatment options at this stage. A recent publication by Thakore et al., describes situations where effective therapies are considered not cost-effective, even if applied at zero cost, due to the substantial cost of background care. UCB encourages ICER to consider multiple perspectives on cost-effectiveness, in addition to customary approaches, when necessary, to accurately assess the value of a treatment.

b. We ask that ICER clarify how short-term clinical trial data will be extrapolated over the course of the economic analysis. Additionally, in the absence of any reference to relative clinical efficacy (e.g., network meta-analysis), we encourage ICER to address how it plans to address relative efficacy, level of uncertainty given the small sample, short duration, and heterogeneity of clinical data.

b. UCB supports ICER's approach to consider a co-base case scenario that includes productivity and "other indirect costs," such as societal perspective. Given the high burden and impact to caregivers, priority should be given to developing an economic analysis (and respective model) that incorporates all relevant value attributes, for both the patient and the caregiver. While UCB acknowledges that the data necessary for such a comprehensive analysis may not be fully feasible, we believe inclusion of this information is a crucial part of the evaluation that will enable a more thorough and appropriate assessment of the value of a treatment.

Inspired by patients.
Driven by science.

c. UCB seeks clarification on how ICER will address health-related quality of life and cost effects for caregivers (e.g., spillover effects). As ICER evolves its assessment, UCB urges ICER to consider the extensive body of literature that characterizes the caregiver burden with respect ALS, accounting not only caregiver time costs, but also, spillover health impacts for caregivers.

d. As ICER finalizes the list of "other outcomes," UCB asks that a change from the baseline of slow vital capacity be considered as it can independently predict loss of functionality and decline of other key respiratory measures.

* * *

UCB appreciates this opportunity to comment on ICER's Draft Background and Scoping Document and welcome further discussion with ICER on this matter. Please contact Amanda Ledford, Director of U.S. Public Policy, at Amanda.Ledford@UCB.com or 202-893-6194 with any questions or feedback on our comments.

Sincerely,

Edward Lee, PharmD
Head of U.S. Health Economics and Outcomes Research Strategy
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080
Edward.Lee@UCB.com