AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis

Revised Background and Scope

March 4, 2022

Background

Amyotrophic lateral sclerosis (ALS) is a rare, progressive, neurodegenerative disease characterized by loss of motor neurons in the brain and spinal cord.[1] ALS often begins with localized weakness that will progress to involve most muscles. People with ALS typically die from respiratory muscle paralysis three to five years after symptom onset.[1] The total annual cost to society for ALS is estimated to be $1 billion, with the highest costs including caregiving, ventilatory support, and hospital care;[2,3] these estimates may underestimate total costs as they may not fully account for unpaid caregiving.

The clinical presentation of ALS is quite varied depending on which motor neurons are affected. Loss of (upper) motor neurons in the brain cause muscle stiffness and spasticity. Significant involvement of frontopontine motor neurons in the brain causes emotional lability (pseudobulbar palsy) with excessive or inappropriate laughing or crying. Loss of (lower) motor neurons in the brainstem and spinal cord leads to muscle twitching (fasciculations) and eventually muscle atrophy. ALS most commonly begins in the limbs, although one of third of individuals have bulbar onset with difficulty chewing, speaking, or swallowing. In addition to muscle involvement, about 50% of people with ALS have cognitive impairment and 15% develop frontotemporal dementia, characterized by progressive cognitive impairment and behavioral changes.[4-6]

Annually, approximately two per 100,000 persons are diagnosed with ALS.[7] Based on the U.S. National ALS Registry, there are an estimated 16,500 people living with ALS in the United States, with a prevalence of five to six per 100,000 persons.[8] However, because of incomplete reporting in the Registry, there may be as many as 30,000 people living with ALS.[9,10] While the etiology of ALS is unknown, it is thought to be due to a combination of genetic predisposition, environmental exposures, and aging-related dysfunction. ALS is mostly sporadic (occurring in the absence of a family history), but 10% of cases are familial.[1] Even among sporadic cases, genetic susceptibility is implicated in ALS pathogenesis.[11,12] The strongest risk factor of developing ALS is increasing age, with the highest prevalence in persons 60 to 79 years old. ALS is more common among men than women, but this difference decreases with advancing age.[13] White race is associated with greater age-adjusted risk of ALS, but these disparities may be exaggerated due to underreporting of ALS

among racial and ethnic minorities.[10,14] Military personnel also have an increased risk of ALS, irrespective of branch, time period served, and duration of enlistment.[15,16]

The diagnosis of ALS is based primarily on clinical evaluation and electromyographic studies. There are no validated surrogate biomarkers or hallmark radiographic findings. Because ALS is a heterogenous disease and requires expert clinical assessment, diagnosis is often delayed by about one year after initial symptom onset.[17,18]

There is no curative treatment for ALS. As such, the management of ALS is largely supportive, including symptomatic treatment, nutritional support (via percutaneous endoscopic gastrostomy) to stabilize weight, and noninvasive ventilation to treat respiratory insufficiency.[19] Increasingly, ALS care is delivered in specialized multidisciplinary centers.[20] By providing comprehensive care across a range of clinical disciplines, the multidisciplinary care approach in ALS is thought to improve quality of life and may extend survival.[19]

There are two Food and Drug Administration (FDA) approved disease-modifying treatments, riluzole and edaravone. Riluzole, which is believed to target glutamate activity, is an oral therapy taken twice daily that modestly slows the progression of disease and is the only approved drug that prolonged survival in clinical trials (average of two to three months).[19,21-23] Edaravone, which is thought to reduce oxidative stress, is currently administered as an intravenous infusion. The initial treatment cycle consists of daily infusions for 14 days followed by a 14-day drug-free period; subsequent cycles require daily infusions for 10 of the 14 days followed by a 14-day drug-free period.[24] Edaravone may modestly slow functional impairment in a subset of ALS patients, but its evidence is more mixed.[25-28]

Two additional pharmacotherapies are being considered for FDA approval in 2022. The first, AMX0035, is an oral combination of two drugs, sodium phenylbutyrate and taurursodiol, and is administered daily for three weeks and twice a day thereafter. This combination therapy is hypothesized to target two different potential mechanisms of neurodegeneration, endoplasmic reticulum stress and mitochondrial dysfunction. AMX0035 is under FDA review with an expected decision date by June 29, 2022.[29] The second is an oral suspension version of edaravone with an identical dosing schedule as its intravenous formulation.[30] Oral administration would potentially overcome many of the burdens and logistical challenges of intravenous infusion of edaravone. Oral edaravone is under FDA review with an expected decision date on May 12, 2022.[31]

Stakeholder Input

This Revised Scoping Document was developed with input from diverse stakeholders, including patients and their families, clinicians, and researchers. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and feedback on the Draft Scope by patient advocacy groups and manufacturers. ICER looks forward to

continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Patients, caregivers, and ALS advocacy groups emphasized that maintaining mobility and the ability to perform routine activities are what matter most to people with ALS and noted a profound burden on caregivers. They were uniformly enthusiastic for more therapeutic options and expressed a high tolerance for adverse effects given the heterogenous, rapidly progressive, and terminal nature of the disease, even if the potential benefits of a new drug were modest. However, treatment burden and costs were cited as major factors in whether they would try new therapies with modest benefits. These stakeholders were also enthusiastic for new drugs because of limited and potentially inequitable access to specialized multidisciplinary ALS centers.

Clinicians were similarly enthusiastic about the need for novel therapeutics for ALS and were especially optimistic about novel agents with different mechanisms of action given the disease heterogeneity. There was consensus among clinical experts that a two-point reduction on the ALS functional rating scale in a single domain would be a dramatic benefit (i.e., being able to walk with some difficulty vs. inability to walk). Though more modest, some clinicians thought a one-point reduction in a single domain is still meaningful and desirable for people living with ALS. Clinicians considered riluzole to be standard of care. However, the use of intravenous edaravone by patients they cared for was quite varied (from <5% to 60% of their patients). Clinicians generally believed an oral formulation of edaravone would be used by more patients. Clinicians emphasized that multidisciplinary care has emerged as the optimal standard of care for ALS.

Manufacturers and trial investigators emphasized a broad indication for treatment using all available therapies as early as possible in persons living with ALS given the high unmet need, questioned the validity of plasma neurofilament levels as a biomarker for treatment response, and highlighted the importance of long-term follow-up data in understanding therapeutic efficacy.

As a result of feedback on the Draft Scope, our scope was revised to clarify the background (costs, prevalence, and risk factors) and scope of our clinical evidence review. Specifically, we modified the subgroups of interest, clarified that we will not make indirect or direct comparisons between AMX0035 and edaravone, and expanded the patient-important outcomes.

Report Aim

This project will evaluate the health and economic outcomes of AMX0035 and oral edaravone for ALS. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events (AEs). Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. We anticipate that some of the evidence for oral edaravone may be indirect evidence from trials of IV edaravone. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of interest for this review is adult persons with ALS.

Data permitting, we intend to examine subgroups defined by:

- Time since symptom onset
- ALS disease onset (bulbar or limb onset)
- ALS etiology (sporadic or familial)
- ALS severity at baseline
- ALS progression
- Race/ethnicity
- Age

Interventions

The two interventions of interest for this review are:

- AMX0035 (Amylyx Pharmaceuticals, Inc.)
- Oral edaravone (Mitsubishi Tanabe Pharma Development America, Inc.)

Both interventions will be evaluated as add-on therapy to standard of care. Standard of care involves multidisciplinary care and may involve treatment with riluzole; in the case of AMX0035, it may also involve treatment with IV edaravone. We do not anticipate comparing the net clinical benefit between AMX0035 and edaravone.

Comparators

We plan to compare to both interventions to standard of care alone as defined above.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - ALS-related functional rating scales (e.g., ALS Functional Rating Scale-Revised [ALSFRS-R] or modified Norris Scale) and their components
    - Mortality
    - Need for non-invasive respiratory support
    - Need for intubation/tracheostomy
    - Need for nutritional support
    - Need for mobility support
    - Need for speech support
    - Hospitalization
    - Quality of Life
    - Caregiver impact
    - AEs
        - Serious AEs
        - AEs resulting in discontinuation of therapy
        - Other AEs

- Other Outcomes
    - Objective measures of strength
    - Measures of respiratory function

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months duration.

Settings

All relevant settings will be considered, including both inpatient and outpatient.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of AMX0035 and oral edaravone. Both AMX0035 and oral edaravone will be evaluated as add-on therapies relative to standard of care as defined above.

The model structure will be based in part on a literature review of prior published models of ALS.[32-34] The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted

life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults with sporadic or familial ALS. Data permitting, we intend to examine subpopulations including, but not limited to, ALS disease onset (bulbar or limb onset) and ALS etiology (sporadic or familial). The model will consist of health states based on disease severity from clinical trial results. A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness may be estimated for shorter time horizons (e.g., five years). A discount rate of 3% per year will be applied to all costs and outcomes.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using best available evidence.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. The health outcome of each intervention will be evaluated in terms of ambulatory time, life-years gained, QALYs gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious AEs. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious AEs. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per year of ambulation gained.

In separate analyses, we will explore the potential health care system budgetary impact of AMX0035 and oral edaravone over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by AMX0035 and oral edaravone, such as need for respiratory support, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of ALS beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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