REPORT AT A GLANCE: **AMYOTROPHIC LATERAL SCLEROSIS**

THEMES AND RECOMMENDATIONS

	AMX0035 (Amylyx Pharmaceuticals, Inc.)	oral edaravone (Mitsubishi Tanabe Pharma America Inc.)
Evidence Rating	C++, when compared to standard of care	For patients who meet the narrowly defined criteria of the clinical trials: C+ For patients who do not meet these criteria, ICER rated the evidence to be insufficient ("I")
Estimated Course Price	Placeholder price of $169,000 per year	$171,000 per year
Annual Health-Benefit Price Benchmark	$9,100 – $30,700 per year	$1,400 – $3,200 per year

"The votes of the Midwest CEPAC reflected the remaining uncertainties around the benefits of these therapies and the overwhelming certainty that $170,000 per year is much too high a price for either therapy despite the overwhelming need for treatments for this devastating disease. The evidence suggests that AMX0035 extends life, and it is clear that oral edaravone is far less burdensome than its infused preparation, but prices need to be greatly reduced to align with benefits."

– ICER's Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- For conditions that are rapidly progressive and fatal, considering FDA approval of drugs on the basis of a single trial that shows benefit in clinically meaningful patient-centered outcomes is not unreasonable. However, there are known risks to approving drugs on the basis of such limited evidence, and if the FDA wishes to follow this course with AMX0035 and other drugs in similar circumstances, it should be more formal in creating a specific, well-defined pathway for conditional approval.
- Manufacturers should seek to set prices of new medications that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments, and not based on the price of existing ALS medications. This is especially important for ALS since new drugs are anticipated to be used in combination with other very expensive drugs, creating the highest risk for financial toxicity due to health care costs.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Amyotrophic lateral sclerosis (ALS) is a rare, rapidly progressive, and fatal neurodegenerative disease characterized by loss of motor neurons in the brain and spinal cord. ALS most commonly presents with localized weakness that progresses to muscle paralysis, respiratory failure, and death. In addition to weakness, up to 15% develop frontotemporal dementia. The etiology of most ALS is unknown. In the United States, there are approximately 25,000 people living with ALS. Age is the strongest risk factor for developing ALS, with the highest prevalence between 60 and 79 years of age. The average life expectancy is three to five years after symptom onset. As the disease progresses, there is a considerable need for caregiving, both paid and unpaid, with significant caregiver burden.

Current treatment of ALS is largely focused on supportive care, which includes symptom management, nutritional support, and noninvasive ventilation to treat respiratory failure, ideally provided in a multidisciplinary ALS clinic. Riluzole and edaravone (Radicava®) are the only two Food and Drug Administration (FDA)-approved therapies that modestly slow disease progression, and riluzole is the only drug thought to prolong survival (average of two to three months). Most patients take riluzole, but edaravone has been used much less because of the burden of intravenous infusion. The FDA recently approved an oral formulation based on bioequivalence with the IV formulation. AMX0035, an oral combination of sodium phenylbutyrate (PB) and taurursodiol (TURSO) taken up to twice daily, is under FDA review with an expected decision date by September 29, 2022.

AMX0035 was evaluated in the CENTAUR trial, a 24-week randomized controlled trial (RCT), and in the companion open-label extension, CENTAUR-OLE. The primary outcome was progression of ALS, and treatment moderately reduced progression, although the statistical significance of this reduction varied depending on the analysis. As a secondary outcome, CENTAUR-OLE assessed death based on the original randomization in CENTAUR, a conservative analysis, and found a 4.8-month survival benefit (hazard ratio 0.64, p=0.048). AMX0035 appears to have minimal harms.

The evidence base for the efficacy of oral edaravone was derived from three RCTs of intravenous edaravone: Studies 16 (early-stage ALS), 18 (late-stage ALS), and 19. Studies 16 and 18 showed no benefit of edaravone on progression of ALS, however a post-hoc analysis of Study 16 raised the possibility of benefit in a narrow subgroup of early-onset ALS patients. Treatment of this subgroup was evaluated in Study 19, and edaravone moderately reduced progression. There were too few deaths to assess survival, however an observational study of edaravone found no evidence of a reduction in mortality. Oral edaravone appears to have minimal harms.

Clinical experts are divided on whether AMX0035 is effective. Nearly all, whether they favored FDA approval or not, felt that only an additional RCT would answer whether AMX0035 actually affects disease progression and survival in ALS. Although there were methodologic concerns with CENTAUR, the OLE raises the possibility of important survival benefits; harms of AMX0035 appear minimal. We rate AMX0035 added to standard of care as comparable or better compared to standard of care alone ("C++").

Two of three trials of IV edaravone were negative. The positive trial was small and of short duration. Most clinical experts we spoke with doubted the efficacy of edaravone and felt that the burdens of the intravenous formulation outweighed any

Clinical Analyses

potential clinical benefit. Oral edaravone is much less burdensome but is labeled broadly for patients with ALS. For patients who meet the narrowly defined criteria of Study 19 we rate oral edaravone added to standard of care to be comparable or incremental compared to standard of care alone ("C+"). However, for patients who do not meet these criteria, we rate the evidence to be insufficient ("I").

Table 1. Evidence Ratings

Treatment	Comparator	Evidence Rating
AMX0035	Standard of Care	C++
oral edaravone	Standard of Care (and meets criteria of Study 19)	C+
	Standard of Care (and does not meet criteria of Study 19)	Insufficient (I)

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We developed a de novo decision analytic model that evaluated hypothetical cohorts of patients with ALS using utility estimates derived from such patients. A placeholder price equal to that of IV edaravone was used for AMX0035. The efficacy of oral edaravone was assumed to be the same as for IV edaravone.

Over a lifetime time horizon, treatment with AMX0035 in addition to SOC resulted in incremental quality adjusted life years (QALYs) and equal value life years (evLYs) of approximately 0.14 and 0.31, respectively. Treatment with oral edaravone in addition to SOC resulted in incremental QALYs and evLYs of approximately 0.04 and 0.05, respectively.

The incremental cost effectiveness of oral edaravone far exceeded typical cost-effectiveness thresholds across multiple analyses and, if priced similarly to edaravone, the incremental cost effectiveness of AMX0035 would also far exceed typical thresholds. The health benefit price benchmark (HBPB) for oral edaravone is $1,400 to $3,200 annually, and the HBPB for AMX0035 is $9,100 to $30,700 annually.

There is tremendous need for new therapies for ALS, a disease that rapidly leads to severe disability and death in many patients. Given this context, pricing at the high end of – or even beyond – traditional cost-effectiveness ranges might be considered. However, given the substantial remaining uncertainties about the benefits of AMX0035 and whether the inexpensive TURSO component of AMX0335 is as effective as the combination of PB and TURSO, if AMX0035 receives regulatory approval while another randomized trial is underway, policymakers should debate short-term pricing options including a far lower price close to the cost of production until the benefits of treatment can be adequately evaluated.

Economic Analyses

POTENTIAL BUDGET IMPACT

Assuming the placeholder price and a 20% uptake of AMX0035 each year (for 50% of eligible patients given that we are assessing two new market entrants), all patients could be treated over five years before reaching the ICER potential budget impact threshold of $734 million per year.

Assuming a 20% uptake of oral edaravone each year (for 50% of eligible patients given that we are assessing two new market entrants), 97% of patients could be treated over five years before reaching the ICER potential budget impact threshold of $734 million per year.

Public Meeting Deliberations

VOTING RESULTS

- A majority of panelists found (11-4) found the evidence is **adequate** to demonstrate a net health benefit when AMX0035 plus standard of care is compared to standard of care alone.

For adults with ALS who **meet** the narrow Study 19 criteria:

- A majority of panelists found (13-2) that the evidence is **adequate** to demonstrate a net health benefit when oral edaravone plus standard of care is compared to standard of care alone.

For adults with ALS who **do not meet** the narrow Study 19 criteria:

- A majority of panelists found (13-2) that the evidence is **not adequate** to demonstrate a net health benefit when oral edaravone plus standard of care is compared to standard of care alone.

During their deliberations, panel members also weighed the therapy's other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- 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 of ALS on individuals
- 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 with oral edaravone given the complexity of treatment with IV edaravone

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations, the Midwest CEPAC evaluated the long-term value both therapies at current pricing (edaravone) and pricing estimates (AMX0035):

- A majority (13-2) of panelists found that AMX0035 represents "low" long-term value for money.
- A majority (14-1) of panelists found that oral edaravone represents "low" long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).