AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis

Draft Evidence Report

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Prepared for

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Anil Makam served as the lead author for the report and wrote the background, comparative clinical effectiveness, and potential other benefits and contextual considerations sections of the report. Dmitriy Nikitin and Rasheed Mohammed led the systematic review with support from Avery McKenna and contributed to the associated sections in the comparative clinical effectiveness chapter. Kangho Suh developed the cost-effectiveness model and authored the corresponding sections in collaboration with Josh Carlson. Marina Richardson developed the budget impact model and provided oversight of the cost-effectiveness analyses. Steven Pearson and David Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Maggie O'Grady and Grace Sternklar for their contributions to this report.

About ICER

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2022/03/ICER_ALS_Stakeholder-List_030322-1.pdf

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List of Acronyms and Abbreviations Used in this Report

AAN	American Academy of Neurology
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ATLIS	Accurate Test of Limb Isometric Strength
ASP	Average sales price
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CALS	Canadian ALS Research Network
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CSF	Cerebrospinal fluid
DB	Double blind
EFNS	European Federation of Neurological Societies
evLY	Equal value life year
FAS	Full analysis set
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FVC	Forced vital capacity
GDP	Gross domestic product
HR	Hazard ratio
HTA	Health technology assessment
ITT	Intention to treat
IQR	Interquartile range
IV	Intravenous
LS	Least squares
LOCF	Last observation carried forward
MCID	Minimal Clinically Important Difference
mITT	Modified intent to treat
MMRM	Mixed measures
MTPA	Mitsubishi Tanabe Pharma America
NEALS	Northeast Amyotrophic Lateral Sclerosis consortium
OLE	Open label extension
PB	Phenylbutyrate
PEG	Percutaneous endoscopic gastronomy
pNF-H	Phosphorylated Neurofilament heavy chain
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SOC	Standard of Care
SVC	Slow vital capacity
TURSO	Taurursodiol
USPSTF	US Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

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.[1] 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.[2] 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.[1] 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 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").

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 0.24 and 0.54, respectively. Treatment with oral edaravone in addition to SOC resulted in incremental QALYs and evLYs of approximately 0.04 and 0.06, respectively.

The incremental cost effectiveness of oral edaravone far exceeded typical cost-effectiveness thresholds across multiple analyses. For instance, in the conventional base-case analysis from the health care system perspective, the incremental cost per QALY gained and evLY gained were approximately $11.99 million and $8.19 million, respectively.

If priced similarly to edaravone, the incremental cost effectiveness of AMX0035 would also far exceed typical thresholds, however its actual cost effectiveness will depend on its price and on confirmation of its clinical benefits. 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.

1. 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 can progress to involve most voluntary muscles. People with ALS typically die from respiratory failure due to respiratory muscle paralysis within 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;[3,4] these estimates may underestimate total costs as they may not fully account for unpaid caregiving and loss of household income.

The clinical presentation of ALS varies 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 some degree of cognitive abnormalities detected on neuropsychiatric testing and 15% develop frontotemporal dementia, characterized by progressive cognitive impairment and behavioral changes.[5-7]

Annually, approximately two per 100,000 persons are diagnosed with ALS.[8] Based on the US National ALS Registry, there are an estimated 24,800 people living with ALS in the United States, with a prevalence of five to six per 100,000 persons.[2] However, because of incomplete reporting in the Registry, an alternate ascertainment method estimated 31,800 people living with ALS.[2,9]

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.[10,11] Studies of twins estimate the heritability of sporadic ALS to be 60% despite an absence of family history.[12] At least 25 genes thus far have been reproducibly implicated in ALS pathogenesis, and broadly cluster within three major (but not mutually exclusive) categories: protein homeostasis (i.e., *SOD1*), RNA homeostasis and trafficking (i.e., *C9ORF72*), and cytoskeletal dynamics.[1] Dysfunction in each of these three pathophysiologic processes result in a diverse array of cellular abnormalities that ultimately lead to neuronal death. Therefore, effective therapy of ALS is likely to require targeting multiple pathways.

Beyond genetic determinants, there are several recognized risk factors for ALS. The strongest risk factor of developing ALS is increasing age, with the highest prevalence in persons 60 to 79 years old (incidence of 32-34 persons per 100,000).[13] ALS is more common among men than women (about

twofold), but this difference decreases with advancing age.[14] 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.[9,15] Military personnel also have an increased risk of ALS, irrespective of branch, time period served, and duration of enlistment.[16,17]

The diagnosis of ALS is based primarily on clinical evaluation, supported by electromyography, neuroimaging, and nerve conduction studies to corroborate the diagnosis and exclude other causes. Neurofilament levels can predict prognosis.[18] However, there are no validated biomarkers or hallmark radiographic findings. Because ALS is a heterogenous disease and requires expert assessment, diagnosis is often delayed by about one year after symptom onset.[19,20] Older age, bulbar onset, faster progression, decreased lung capacity, diagnostic delay, and frontotemporal dementia indicate worse prognosis.[21,22]

There is no curative treatment for ALS. As such, the management of ALS is largely supportive, including symptomatic treatment and, when necessary, nutritional support (via percutaneous endoscopic gastrostomy) to stabilize weight and noninvasive ventilation to treat respiratory insufficiency (See Supplement C for additional clinical guidelines).[23] Increasingly, ALS care is delivered in specialized multidisciplinary centers.[24] By providing comprehensive care across a range of clinical disciplines, the multidisciplinary care approach in ALS is thought to increase the use of evidence-based therapies, improve quality of life, and may extend survival.[23]

To date, there have been over 80 randomized controlled trials published on ALS therapies and only riluzole and edaravone are approved by the FDA as disease-modifying treatments that modestly slow progression. 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).[23,25-27] Edaravone, which is thought to reduce oxidative stress, has been administered as an intravenous infusion prior to the approval of its oral formulation. 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.[28] Edaravone may modestly slow functional impairment in a subset of early-onset ALS patients with shorter ALS duration and slower rate of progression prior to randomization; but its evidence is more mixed.[29-32] The American Academy of Neurology (AAN) practice guidelines issued in 2009 (and reaffirmed January 11, 2020) recommend riluzole to slow progression, but do not discuss the use of edaravone.[23]

An oral suspension version of edaravone (Radicava ORS®) with an identical dosing schedule to its intravenous formulation was approved by the FDA on May 12, 2022.[33] Oral administration would overcome many of the risks, burdens, and logistical challenges of intravenous administration of edaravone. AMX0035 is an oral combination of two drugs, sodium phenylbutyrate (PB) and taurursodiol (TURSO), that is administered daily for three weeks and up to 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 September 29, 2022.[34]

Table 1.1. Interventions of Interest

Intervention Generic Name (Brand Name)	Proposed Mechanism of Action	Delivery Route
AMX0035	Reduce endoplasmic reticulum stress and mitochondrial dysfunction	Oral sachet taken orally or by feeding tube
Oral edaravone (Radicava ORS®)	Free radical scavenger	Oral suspension, taken orally or by feeding tube

2. Patient and Caregiver Perspectives

ICER engaged with patients, caregivers, representatives from ALS advocacy organizations, and clinical experts to understand perspectives from those living with the disease, their specific challenges and unmet needs, contextual considerations, and outcomes most relevant to patients and the ALS community (See Supplement Section B).

Patients and patient groups particularly emphasized the diverse range of disease experiences, the profound caregiver burden and costs, enthusiasm for novel medications (even those with only modest benefit), concerns about treatment burdens and cost, and disparities in ALS care.

As ALS progresses, patients' wellbeing and quality of life declines.[35] The nature of ALS symptoms and experience of living with the disease depend on which motor neurons are affected and by the rate of progression. Though the impact of ALS on patients and their caregivers is varied, progressive weakness is a core feature of the disease.[36] Inability to perform routine activities and limitations with mobility are among the most common impairments and were rated as having the greatest impact on wellbeing by both patients and caregivers participating in the ALS Focus What Matters Most Survey.[37] If ALS involves bulbar motor neurons, then difficulties chewing, swallowing, or speaking may predominate. After the onset of respiratory failure, patients report considerable breathlessness.[36] People with ALS also suffer from a range of other debilitating nonmotor symptoms,[38] including psychiatric symptoms, such as depression, and cognitive impairment, especially if frontotemporal dementia develops. Although ALS is typically relentlessly progressive, about 10% of patients experience a slow rate of progression and survive for longer than 10 years.[21]

Caregiver needs and burden in ALS are profound. As the disease progresses, there is greater need for informal and paid caregiving.[39] Among 600 caregivers participating in the ALS Focus Caregiver Survey, 68% reported spending more than 30 hours per week providing care and nearly half felt unprepared for changes in caregiving responsibilities as ALS progressed.[40] Caregivers experience greater stress than people living with ALS because of the emotional, physical, and financial toll.[36] The majority of caregivers report a decline in their own physical and mental health. Patients and their caregivers also face considerable financial stress from both medical and non-medical costs, compounded by loss of household income because of inability to work due to increased unpaid caregiving responsibilities and caregiver burden.[3] As such, one in three caregivers in a national survey report ALS having devastating or a near-devastating financial impact.[36]

Patients, caregivers, and clinical experts were uniformly enthusiastic for more therapeutic options and expressed a high tolerance for adverse effects given the rapidly progressive and terminal nature of the disease, even if the potential benefits of a new drug were modest. These stakeholders also emphasized a desire for a broad indication for treatment and using all available therapies as early as possible in persons living with ALS given the high unmet need. Having multiple

therapies with different mechanisms of action was also reported as a priority because ALS is a heterogenous illness with multiple molecular pathways leading to neuronal death. While, on average, treatment benefits are modest, stakeholders reported that two-points on the revised ALS Functional Rating Scale (ALSFRS-R) in a single domain would be a dramatic change (i.e., being able to walk with some difficulty vs. inability to walk). Though more modest, many reported that even a one-point difference in a single domain is still meaningful and desirable for people living with ALS. There is no research on the clinical significance of ALSFRS-R changes. One survey of 65 ALS experts found that most would consider a change of 20% or greater on the rate of decline of the ALSFRS-R score to be meaningful.[41]

Treatment burden and costs were cited as major barriers in whether patients would try new therapies with limited to modest benefits. This is especially true for patients with slow progressing ALS because of their lower risk tolerance and concern about long-term financial security. Most patients take riluzole, but only some use intravenous edaravone because of the limited evidence for effectiveness, higher costs, burden, and risks of having a central venous catheter, and the time required to travel to infusion centers. Clinical experts also reported varied use of intravenous edaravone in their practice (from <5% to 60% of their patients), and cited opportunity costs for their practice as an additional challenge, which includes time and resources spent securing insurance approval, coordinating infusions, and managing catheter-related complications and infections. In the US, approximately 11% of ALS patients are prescribed intravenous edaravone.[42] Patients and clinical experts alike reported a strong preference in favor of the oral formulation and expressed more willingness to try it.

Patients and patient groups reported challenges with access to care and to clinical trials for ALS, with concerns for health inequities. One particular challenge is access to specialized multidisciplinary ALS clinics, which is considered a standard of care for the treatment of ALS.[23] There are over 200 ALS clinics in the US, 73 of which are Certified Treatment Centers of Excellence by the ALS Association.[43,44] However, ALS multidisciplinary clinics are not geographically distributed—several states have only one or two clinics. Since travel to a multidisciplinary clinic is a major barrier,[45] even for patients living in closer proximity to a clinic, there are concerns for longer diagnostic delays among racial/ethnic minorities, low-income households, and those living in rural areas.[46] Thus, stakeholders expressed enthusiasm for new oral medication treatment options to potentially overcome inequitable access to other treatments, such as experimental therapies that may only be available in specialized multidisciplinary ALS clinics affiliated with academic medical centers.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence of AMX0035 and oral edaravone for ALS are detailed in Supplement D1.

Scope of Review

We reviewed the clinical effectiveness of AMX0035 added on to standard of care versus standard of care alone, defined as multidisciplinary care, ± riluzole, ± intravenous edaravone. Separately, we conducted a review of edaravone as an add-on therapy to standard of care versus standard of care alone, which includes multidisciplinary care ± riluzole.

We examined evidence on patient-important outcomes, including change in disease progression as measured by a functional rating scale, mortality, respiratory function, ALS-related quality of life measures, and adverse events. We also sought data on subpopulations of interest, including bulbar or limb onset ALS, sporadic or familial ALS, and race/ethnicity. The full scope of the review is detailed in Supplement D1.

Evidence Base

Our search identified a total of six references for AMX0035 and 19 references for edaravone. Additionally, we received academic-in-confidence submissions for AMX0035 to supplement publicly available data. The clinical evidence is summarized separately below, as each drug was studied in different populations and the interventions were not compared to each other. Detailed descriptions of the included trials can be found in Supplement Tables D7 and D15.

AMX0035

Evidence to inform our review of AMX0035 was derived from one phase II trial, CENTAUR, and its open-label extension, CENTAUR-OLE.[47,48] We obtained additional results and information about CENTAUR and its OLE from an FDA Advisory Committee Meeting.[49-51] A Phase 3 trial of AMX0035 (PHOENIX) is currently underway and is expected to have topline results in 2024.[52]

Table 3.1 Overview of AMX0035 Key Studies

Study	Design	Treatment Arms	Key Baseline Characteristics
CENTAUR	DB, PC, Phase 2 RCT	N= 137 AMX0035 (89) Placebo (48)	Age (mean): 57.5 years Time since symptom onset (mean): 13.5 months ALS Bulbar Onset: 27% Definite + Probable ALS Diagnosis: 100% Baseline ALSFRS-R (mean): 36.0 Pre-baseline ALSFRS-R slope (mean): 0.94 Concomitant use of riluzole: 71% Concomitant use of edaravone: 34%
CENTAUR-OLE	Single arm, open label extension	N= 90* Originally assigned to AMX0035 (56) Originally assigned to placebo (34)	Refer to key baseline characteristics above

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised, DB: double blind, OLE: open label extension, PC: placebo controlled, RCT: randomized controlled trial
*Survival analysis in OLE included all participants originally randomized in CENTAUR (n=137)

CENTAUR

CENTAUR was a 24-week phase II trial that randomized 137 participants in a 2:1 ratio to AMX0035 (n= 89) and placebo (n= 48). The primary outcome was the rate of decline in the ALSFRS-R score.[47]

CENTAUR-OLE

CENTAUR-OLE aimed to assess the longer-term safety and efficacy of AMX0035. Participants were eligible to enter the OLE if they completed all visits required during the CENTAUR trial. Overall, 66% of patients originally randomized enrolled into the OLE, which included 56 (64%) from the AMX0035 arm and 34 (71%) from the placebo arm of the CENTAUR trial. During the OLE, all enrolled participants were eligible to receive AMX0035 for up to 30 months (132 weeks). To preserve blinding of the original treatment assignment in the randomized phase, participants were administered the same dose that they received at the end of the CENTAUR trial.[48]

Secondary outcomes of the OLE included rate of key events, including tracheostomy, hospitalization, and death (all-cause) between participants originally randomized to AMX0035 (n=89) versus placebo (n=48), including participants who did not enroll in the OLE.[48] For participants not enrolled in or dropped out of the OLE, vital status was assessed through an evaluation of public records of deaths (i.e., Social Security Death Index). The CENTAUR-OLE publication applied a cut-off date of July 20, 2020 for ascertainment of deaths.[48] Survival analysis using a more recent cut-off date of March 1, 2021 were made available and were used as the primary source of evidence for the OLE in our report. This consists of data from CENTAUR-OLE

supplemented by the FDA briefing document and slide presentations from the FDA Advisory Committee Meeting.[49-51] Additional trial information can be found in Supplement Section D2 and Tables D8 and D10.

Oral Edaravone

Our assessment of oral edaravone is primarily based on the clinical evidence from the MCI-186 clinical trials program of intravenous edaravone (Table 3.2). The manufacturer, Mitsubishi Tanabe Pharma America, has established the bioequivalence between the intravenous (60mg) and oral (105mg) formulations of edaravone in a series of pharmacological studies that were included in its new drug application.[53]

Table 3.2 Overview of Intravenous Edaravone Key Studies[30-32,54,55]

Study	Trial Type	Treatment Arms	Key Baseline Characteristics
MCI186-16 Study 16	DB, PC, Phase 3 RCT	N= 205 Edaravone, IV (101) Placebo (104)	Age (mean): 57.8 years Time since symptom onset (mean): 15.0 months ALS Bulbar Onset: 18.5% FVC: 95.7% Definite + Probable ALS Diagnosis: 76.1% Baseline ALSFRS-R (mean): 40.9 Pre-baseline ALSFRS-R slope (mean): 0.67 points per month Faster progressors*: 29.8% Concomitant use of riluzole: 88.8%
MCI186-18 Study 18	DB, PC, exploratory Phase 3 RCT	N=25 Edaravone, IV (13) Placebo (12)	Age (mean): 58.6 years Time since symptom onset (mean): 22.7 months ALS Bulbar Onset: 12% FVC: 85.1% Definite + Probable ALS Diagnosis: 84% Baseline ALSFRS-R (mean): 33.5 Pre-baseline ALSFRS-R slope (mean): 1.01 points per month Faster progressors*: 32% Concomitant use of riluzole: 84%
MCI186-19 Study 19	DB, PC, Phase 3 RCT	N=137 Edaravone, IV (69) Placebo (68)	Age (mean): 60.3 years Time since symptom onset (mean): 13.2 months ALS Bulbar Onset: 21.9% FVC: 99.0% Definite + Probable ALS Diagnosis: 100% Baseline ALSFRS-R (mean): 41.8 Pre-baseline ALSFRS-R slope (mean): 0.57 points per month Faster progressors*: 16.8% Concomitant use of riluzole: 91.2%

ALS: amyotrophic lateral sclerosis, ALSFRS-R: amyotrophic lateral sclerosis functional rating score-revised, DB: double blind, FVC: forced vital capacity, PBO: placebo, PC: placebo-controlled, RCT: randomized controlled trial
*Faster progressors are defined as participants who had a decrease in their ALSFRS-R score of -4 or -3 points during the trial's 12-week observation period (vs. a -2-to--1-point decline).

MCI-186-16 (herein referred to as "Study 16") was a Phase 3 double-blind placebo-controlled trial that randomized 206 adults with early-stage ALS (Grade 1 or 2 on the Japanese ALS severity classification) to evaluate the effectiveness and safety of intravenous edaravone. Study 16 did not meet its primary endpoint of change in ALSFRS-R score.

MCI-186-18 (herein referred to as "Study 18") was an exploratory Phase 3 double-blind placebo-controlled trial that evaluated the effectiveness and safety of intravenous edaravone versus

placebo in 25 adults with advanced ALS (Grade 3 on Japanese ALS scale and forced vital capacity (FVC) of at least 60%). Study 18 did not meet its primary endpoint of change in ALSFRS-R score.

A post-hoc analysis of the Study 16 trial identified a "definite or probable Greater-Efficacy-Expected Subpopulation within two years" (dpEESP2y) of ALS symptom onset in which edaravone was associated with a statistically significant benefit in slowing decline in the ALSFRS-R score versus placebo. The dpEESP2y subgroup comprised 35% of the randomized population which met more narrow clinical criteria at baseline (shorter ALS duration, greater certainty of diagnosis, and slower rate of progression prior to randomization).

MCI186-19 (herein referred to as "Study 19") was a pivotal Phase 3 double-blind placebo-controlled trial designed to substantiate the post-hoc finding in a prospectively defined population that met the narrower inclusion criteria of the dpEESP2y subgroup. Study 19 inclusion criteria were similar to Study 16 inclusion criteria, except they required having at least two points for all non-respiratory ALSFRS-R items, an FVC of at least 80%, definite or probable ALS per the El Escorial and revised Airlie House diagnostic criteria, and a disease duration of two years or less since symptom onset. The full inclusion criteria of Study 16, 18, and 19 are detailed in Supplement Table D4.

Our assessment of the efficacy of edaravone was supplemented with additional analyses conducted by the FDA's Office of Drug Evaluation and the Canadian Agency for Drugs and Technologies in Health (CADTH).[54-56] Additionally, an observational cohort study of 260 ALS patients in Germany provided supportive real-world evidence on the long-term effectiveness (disease progression and survival probability) of intravenous edaravone.[57]

Safety outcomes of intravenous edaravone were assessed using a pooled safety analysis of Study 16, 18 and 19, and the SUNRISE Japan post-marketing surveillance trial.[58,59] Safety outcomes for oral edaravone were based on preliminary findings from Study MT-1186-A01, a 48-week open-label safety trial.[60] These studies are described in detail in Supplement Section D2.

An ongoing randomized Phase 3 trial, MT-1186-A02, is evaluating the effectiveness and safety of two oral edaravone dosing strategies, the standard on-off cycling treatment of intravenous edaravone versus daily dosing of oral edaravone.[61,62] Results from this trial are expected in 2023-2024. This and other ongoing trials are described in Supplement Section D3.

3.2. Results

Clinical Benefits

The primary endpoint for all AMX0035 and intravenous edaravone trials was the change in the revised ALS Functional Rating Scale (ALSFRS-R) at 24 weeks. The ALSFRS-R is a validated 48-point measure to assess a person's function and ability to maintain daily activities across 12 individual

components within four domains: bulbar, fine motor, gross motor, and respiratory. The minimal clinically important difference for the ALSFRS-R is unknown. However, ALS clinical experts believe a change of 20% or greater on the rate of decline of the ALSFRS-R score is meaningful, and patients we spoke with considered even a 1-point change to be modest but still important (see Section 2.1 for details).[41] For AMX0035, survival was included in a composite secondary outcome of time to death, tracheostomy, permanent assisted ventilation (PAV), or hospitalization. For edaravone in Study 19, survival was included in a composite outcome of time to death or disease progression.

Other secondary trial endpoints included rate of decline of respiratory function (slow and forced vital capacity), other measures of functional status (Modified Norris scale), objective measures of strength [pinch strength, grip strength, Accurate Test of Limb Isometric Strength (ATLIS)], exploratory biomarkers, and quality of life [40 item ALS Assessment Questionnaire (ALSAQ-40)] (Supplement Tables D11, D22, D23). There was no available evidence on patients' need for nutritional, mobility, or speech support, or on caregiver burden. See Supplement Section A for further definitions of key outcomes.

AMX0035

Slowing of ALS-related Functional Decline

In the modified intention to treat (mITT) analysis of the CENTAUR trial, the mean ALSFRS-R score at week 24 was 29.06 in the AMX0035 arm and 26.73 in the placebo arm; resulting in a difference of 2.32 points (95% CI: 0.18 to 4.47, p=0.034), which represented a 25.3% slowing of ALS disease progression over this time period.[47,49] However, this mITT analysis was potentially problematic because it excluded two early deaths in the AMX0035 arm who received doses but did not complete a post-baseline ALSFRS-R assessment, assumed linearity in ALSFRS-R decline, and ignored deaths in the assessment of function. In a joint rank analysis conducted by the FDA (which combines function and survival into a single measure) using the ITT population (including the two early deaths) and multiple imputation for missing data, the result favored AMX0035, but was not statistically significant (rank of 12.0, p=0.079).[49]

Sensitivity and Exploratory Analyses of ALSFRS-R

Additional sensitivity analyses were carried out by the manufacturer and FDA to assess the robustness of the ALSFRS-R results, with FDA models showing lower efficacy and less persuasive statistical significance (see Table 3.3). Sensitivity analyses conducted by the manufacturer that accounted for concomitant use of riluzole and intravenous edaravone were qualitatively similar to the primary analysis (Supplement Table D13). In an exploratory analysis, the effect was seen across all four subdomains, and was most prominent for the fine-motor subscale, which includes handwriting, cutting food, and dressing and hygiene (Supplement Table D9).

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

	Amylyx				FDA	
	AMX0035	**Placebo**	**Difference**	**95% CI; p-value**	**Difference**	**p-value**
Primary*	29.06 (0.78)	26.73 (0.98)	2.32	(0.18 to 4.47); 0.03	1.68 (1.06)	0.11
Change in Baseline*	-6.70 (0.68)	-9.62 (0.91)	2.92	(0.70, 5.15); NR	1.86 (1.04)‡	0.07
Joint Rank, ITT†	73.9 (3.9)	59.9 (5.3)	13.99 (6.6)	NA; 0.037	12.0 (6.82)	0.079

CI: confidence interval, FDA: Food and Drug Administration, ITT: intention to treat, NA: not available, NR: not recorded

* Amylyx assumed linearity in mITT population; FDA used non-linearity assumption in mITT population. Least squares mean used to calculate difference for primary outcome and change in baseline.

† Joint Rank: performed by ranking subjects by time to death or death equivalent (permanent assisted ventilation) then by change from baseline in ALSFRS-R. For missing data, Amylyx used last observation carried forward (assumed stable disease progression) and FDA used multiple imputation with a missing at random assumption. Rank estimate used to calculate difference.

‡ FDA used a mean-by-visit mixed model repeated measures approach to calculate difference for change in baseline.

Survival

In the CENTAUR trial, fewer patients in the AMX0035 arm than the placebo arm had a composite outcome of death, tracheostomy, PAV or hospitalization, but this was not statistically significant (19.2% vs. 31%, HR: 0.575, 95% CI: 0.29 to 1.15, p=0.11).[49] During the randomized phase, five patients (6%) in the treatment arm died compared to two patients (4%) in the placebo arm[47] (HR: 1.02, 95% CI: 0.15 to 9.75)[48].

In CENTAUR-OLE, using a July 20, 2020, cutoff date, the difference in median survival between patients originally randomized to AMX0035 versus placebo was 6.5 months (HR: 0.56, 95% CI: 0.34 to 0.92, p=0.023). Using the most recent March 1, 2021 cutoff date to ascertain deaths, the difference in median survival was 4.8 months (23.5 months for AMX0035 versus 18.7 months in the group originally assigned to placebo; HR: 0.64, 95% CI: 0.42 to 0.995, p=0.0475).[49]

Secondary Outcomes

Overall, none of the prespecified secondary endpoints in the CENTAUR trial were statistically significant, although most outcomes were numerically in favor of the AMX0035 arm. The secondary outcomes are further explored in Supplement Section D2.

For the OLE, we did not consider other secondary outcomes (ALSFRS-R, ATLIS scores, SVC, and composite survival endpoint) as we felt the findings were unreliable in the setting of unblinding

during the OLE, and missing data due to incomplete participation and dropouts. These results are outlined in Supplement Table D10.

As of the date of this Report, there are no available data on quality-of-life results for AMX0035. This information is expected to be made available through the ongoing PHOENIX trial.

Oral Edaravone

The primary efficacy endpoint in Study 16, 18, and 19 for intravenous edaravone was the change in ALSFRS-R total score from baseline to end of week 24 (6 months).

Slowing of ALS-related Functional Decline

Table 3.5. Edaravone Key Outcomes at Week 24

	Change from Baseline in ALSFRS-R Score at Week 24		
Trial	**Edaravone** LSM ± SE	**Placebo** LSM ± SE	**LSM Difference,** LSM ± SE (95% CI), p-value
Study 16	-5.70 ± 0.85	-6.35 ± 0.84	0.65 ± 0.78 (-0.90 to 2.19), p=0.411
Study 18	-6.52 ± 1.78	-6.00 ± 1.83	-0.52 ± 2.46 (-5.62 to 4.58), p=0.835
Study 19	-5.01 ± 0.64	-7.50 ± 0.66	2.49 ± 0.76 (0.99 to 3.98), p= 0.0013

ALSFRS-R: amyotrophic lateral sclerosis functional rating score-revised, CI: confidence interval, LSM: least squares mean, SE: standard error

Study 16

Patients treated with intravenous edaravone arm had no statistically significant difference in change in the ALSFRS-R score compared with placebo (Table 3.5).

In a post-hoc analysis of Study 16, there was a modest and statistically significant slowing of disease progression for intravenous edaravone in the dpEESP2y subpopulation (ALSFRS-R difference of 3.01 points, 95% CI: 0.35 to 5.67, p=0.027) (Supplement Table D19). But in the group not meeting the dpEESP2y subpopulation criteria (n=131), patients randomized to edaravone did numerically worse than those treated with placebo, although this was not statistically significant (difference of -0.57 points, 95% CI: -2.55 to 1.41, p=0.57).[54]

Study 18

Among patients in Study 18 with far more advanced ALS than Study 16, there was no statistically significant difference in change in the ALSFRS-R score for treatment with edaravone compared with placebo (Table 3.5).

Study 19

Study 19 only enrolled patients meeting the post-hoc dpEESP2y subgroup inclusion criteria (see Section 3.1 and Supplement Table D4 for details). The primary mITT analysis found that the intravenous edaravone arm had a modest and statistically significant slowing of disease progression (difference of 2.49 points in the ALSFRS-R score at 24 weeks, 95% CI: 0.99 to 3.98, p=0.0013). This translates to a 33% slowing of disease progression in favor of edaravone.

Sensitivity and Exploratory Analyses of ALSFRS-R in Study 19

In Study 19, patients who discontinued the trial before completion of three treatment cycles were excluded from the primary mITT analysis (one in the edaravone arm for a tracheotomy and two in the placebo arm who withdrew consent), and missing values due to loss to follow up were imputed assuming stable disease progression (last observation carried forward). Reassuringly, post-hoc sensitivity analyses of Study 19 conducted by the manufacturer and FDA, including an ITT analysis, supported the robustness of the primary results (Supplement Table D5).

Several post-hoc analyses of Study 19 demonstrated edaravone's benefit over placebo in the ALSFRS-R score (Supplement Section D2).

Survival

There is insufficient clinical trial evidence of intravenous edaravone's effect on survival. Collectively, there were six deaths in the 24-week randomized phases of Study 16, 18, and 19: four patients randomized to edaravone (2.2%) and two patients to placebo (1.1%), all of whom died from respiratory failure due to ALS progression.[58] There were zero deaths in Study 19. During the 24-week open-label extension of Study 19, survival was not prespecified, and only three participants died (one in the edaravone-edaravone arm and two in the placebo-edaravone arm).[63]

In the absence of clinical trial evidence, an observational cohort study of 130 ALS patients treated in twelve German ALS multidisciplinary centers who completed at least four treatment cycles of intravenous edaravone found no difference in disease progression (p=0.37) or survival at 18 months compared to 130 patients in the propensity score–matched control group who received standard of care (25% vs. 25%, log rank p=0.63).[57] A subgroup analysis among patients who met five or six of the Study 19 inclusion criteria was similar (log rank p=0.95 for survival).

Secondary Outcomes

Study 16 and 18 did not meet any of their secondary endpoints (See Supplement Table D22).

For Study 19, secondary endpoints numerically tended to favor the intravenous edaravone group. The only statistically significant differences between edaravone and placebo were for the Modified Norris Scale score (an alternate ALS functional scale) and for quality of life (ALSAQ-40 score).

The Modified Norris Scale is an alternate rating scale that assesses limb and bulbar function. Patients with a greater Modified Norris Scale score (range 0-102) report better functioning across the 21 and 13 limb and bulbar items, respectively. Study 19 participants treated with edaravone reported less decline in the total Modified Norris Scale versus placebo (difference of 4.89 points, 95% CI: 0.24 to 9.54, p=0.039). The between-group score differences among the individual limb and bulbar scores were not statistically significant (Supplement Table D22).

The ALSAQ-40 is a self-reported measure of ALS-related quality of life. Persons with a greater ALSAQ-40 score (range: 40-100) report greater difficulties on activities of physical mobility, daily living and independence, eating and drinking, communication, and emotional reactions. In Study 19, the intravenous edaravone group had less decline in ALSAQ-40 (mean difference of -8.79, SE: 4.03, p=0.03).

There is no established minimal clinically important difference (MCID) for the Modified Norris Scale or the total ALSAQ-40 score.[55]

Harms

Both AMX0035 and oral edaravone have a low risk profile for adverse drug events.

AMX0035

The most common adverse event in patients enrolled in the CENTAUR trial was gastrointestinal disorder which occurred in 59 (66.3%) patients randomized to AMX0035 versus 30 (62.5%) patients randomized to placebo. The two most common adverse events that occurred in a greater proportion of patients treated with AMX0035 than placebo were diarrhea (21.3% vs. 16.7%) and nausea (18% vs. 12.5%). These gastrointestinal adverse risks were greater in the AMX0035 arm during the first two weeks of the trial (32.6% vs. 20% of patients in the placebo arm).[49] There were more cardiac events in the AMX0035 arm (8% vs. 0%), but detailed review found these to be largely clinically insignificant and unlikely related to the drug. Supplement Table D12 provides a detailed list of adverse events.

Oral Edaravone

The majority of safety data for edaravone are from studies of intravenous edaravone. Pooled safety data from Studies 16, 18, and 19 showed a similar rate of adverse events (87.5% vs. 87%). The three most common adverse events that occurred in a greater proportion in the intravenous edaravone arm versus placebo were contusion (14.7% vs. 8.7%), gait disturbance (12.5% vs. 9.2%), and headache (8.2% vs. 5.4%). The incidence of treatment-related adverse events that led to discontinuation was lower in the edaravone arm than placebo (2.2% vs. 5.4%). Of note, harms from the intravenous administration of a therapy to patients with ALS would be unlikely to have been detected in this study design as events were compared with patients receiving placebo infusions.

Preliminary results from the 24-week open-label international multicenter safety study of oral edaravone were generally consistent with the adverse events observed in the intravenous edaravone arm of the MCI clinical trials, and most frequently included muscle weakness (16.2%), fall (15.7%), and fatigue (7.6%).[60] The incidence of muscle weakness was greater in the pooled safety study (16.2%) than the collective randomized arms of edaravone (4.3%) and placebo (5.4%). The most notable difference in safety profile is that because of the difference in formulation, oral edaravone does not have any infusion- or catheter-related adverse events, such as contusions.

For real-world safety data, the SUNRISE Japan post-marketing observational surveillance study reported the incidence of adverse drug reactions up to one year after treatment initiation among 800 Japanese ALS patients treated with intravenous edaravone. Abnormal hepatic function was the most frequent adverse drug reaction (4.4%).

Supplement tables D24 and D25 provide a detailed list of adverse events in the clinical trials, SUNRISE study, and preliminary findings for oral edaravone.

Subgroup Analyses and Heterogeneity

AMX0035

There were no publicly available data on subgroup analyses for the CENTAUR trial.

Oral Edaravone

We reviewed evidence from the FDA and CADTH on intravenous edaravone's impact on ALSFRS-R score in Study 19 across several subgroups of interest, including duration of illness (<1 vs. ≥ 1 year), type of ALS onset (bulbar vs. limb), ALS etiology (sporadic vs. familial), baseline ALS severity (ALSFRS-R scores of 42-47 vs. 36-41), and age (<65 vs. ≥ 65). We found no available subgroup analyses for baseline ALSFRS-R progression rate or race/ethnicity (MCI-186 clinical trials program only included Japanese ALS patients). There were no notable differences in ALSFRS-R decline between edaravone and placebo for any of the listed subgroups (Supplement Table D26).

Uncertainty and Controversies

AMX0035

- The evidence for AMX0035 comes from a single small RCT and its extension study. 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.

- CENTAUR enrolled patients who were from the US and overwhelmingly white, raising some concerns about generalizability to other groups. The small sample size of CENTAUR precluded meaningful subgroup analyses.

- There was an implementation error in CENTAUR where the first 17 patients all received edaravone; the next nine were given placebo to balance this. We heard, including through direct conversation with a study nurse, that those administering therapy remained blinded and were unaware of this error, and sensitivity analyses excluding these patients showed similar results for functional outcomes. We requested a similar analysis of survival in the OLE and this, too, showed similar outcomes, although the results are academic-in-confidence.

- Concerns were raised about functional unblinding due to the bitter taste and gastrointestinal side effects of AMX0035 (Supplement Table D14). The survival benefits seen in the OLE would not be expected to have been affected by unblinding.

- The FDA re-analyzed the primary and secondary outcomes of disease progression using the ITT population (which includes two early deaths in the AMX0035 arm), a quadratic term for non-linearity, and a joint-rank approach to incorporate deaths in assessing disease progression. When factoring in these issues, the FDA found consistently lower efficacy and less statistical persuasiveness (See Table 3.3).

- The FDA felt that survival was not a pre-specified endpoint in the OLE trial. Our reading of the protocol is that this is ambiguous. Of note, the method used to analyze survival is conservative as crossover from placebo to AMX0035 was not accounted for; the true survival benefit may be greater than that reported. However, some experts felt that the small functional gains and lack of a survival benefit in the 24-week RCT made a substantial survival benefit highly unlikely to be real.

- Even if AMX0035 is efficacious, it is unknown whether the combination of PB and TURSO in AMX0035 is superior to TURSO alone; TURSO is the cheaper of the two components, currently available as a nutritional supplement, and is already used by some ALS patients. A

pilot RCT of TURSO in 34 ALS patients found the TURSO arm had less decline in ALSFRS-R at 54 weeks.[64] A confirmatory multicenter RCT in Italy is underway and estimated to complete in 2023.[65]

Oral Edaravone

- Two of three trials of IV edaravone were negative. The positive trial is small and of short duration. Most clinical experts we spoke with doubted the efficacy of edaravone and generally felt that the burdens of the intravenous formulation outweighed any potential clinical benefit. Although Study 19 had positive results on function, it did not show benefits on survival and neither did an observational study.

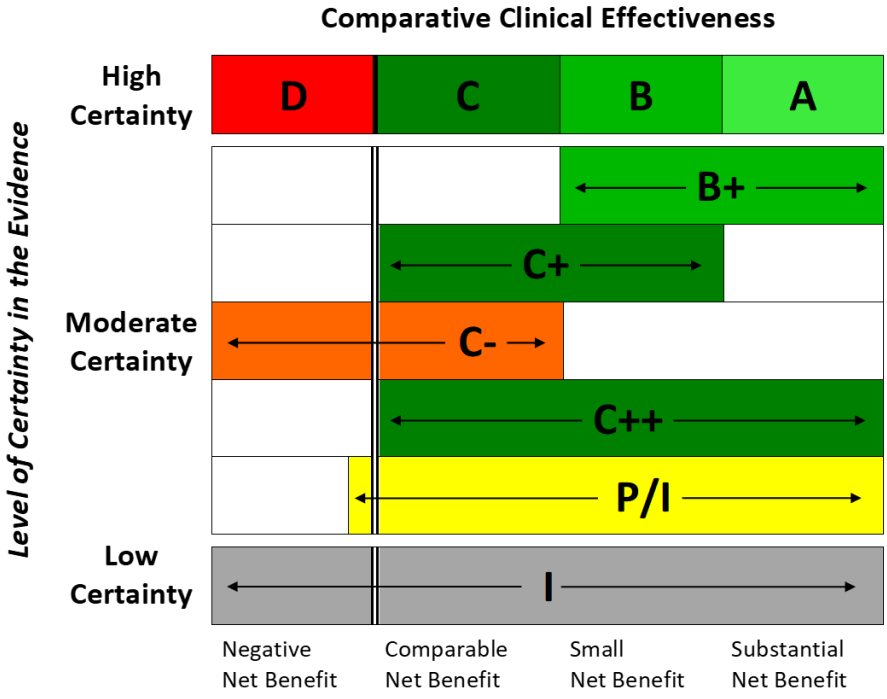
- Intravenous edaravone was only studied in Japan, raising some concerns about generalizability to other groups. The small sample size of Study 19 precluded meaningful subgroup analyses.

- Even if edaravone is effective in the subset of patients found in the post-hoc analysis of Study 16 and evaluated in Study 19, this population only represents up to 10% of all ALS patients.[66-68] Despite this, edaravone has an FDA indication for all patients with ALS.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided on ICER's website.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

AMX0035

The CENTAUR trial and companion OLE demonstrated modest benefits in slowing ALS progression during the randomized phase, as measured by the ALSFRS-R score, and a 5-month survival benefit with longer-term follow-up (or ~40% reduction in the hazard of dying). These benefits constitute a small (progression) to substantial (survival) benefit in ALS, especially in an unrelenting progressive and fatal disease. However, our rating was tempered because the evidence was based on one

small, fair-quality RCT with several methodological concerns, showed lower efficacy for slowing disease progression with less statistical persuasiveness with the use of more appropriate analytic methods, and demonstrated a lack of survival benefit during the blinded randomized phase during the first six months. Since the risks are low, we rate AMX0035 added to standard of care as *comparable or better* compared to standard of care alone ("**C++**").

Oral Edaravone

For patients who meet the narrow Study 19 criteria

The pivotal Study 19 enrolled a selected group of early-stage ALS patients who were required to have: probable or definite ALS within two years of symptom onset and living independently (grade 1 or 2 on the Japan ALS Severity Classification), intact respiratory function with an FVC ≥80% and normal scores on the ALSFRS-R respiratory subscale, good functioning (≥2 points) on all non-respiratory ALSFRS-R items, and evidence of disease progression (decrease of 1-4 points in the ALSFRS-R score) in the preceding 12 week period. In this narrowly defined population, intravenous edaravone showed a decline in the ALSFRS-R score by ~2.5 points, which is considered clinically meaningfully by patients and clinical experts. This finding was consistent across several sensitivity analyses and was supported by several secondary outcomes that modestly favored edaravone (respiratory capacity, quality of life), but not measures of strength. Our rating is tempered by the possibility that with multiple trials, a single trial could be positive due to chance, by experiences of clinical experts who had administered edaravone and doubted its benefit, and by a well-designed observational cohort study that found no difference in progression and survival in real world patients. Since oral edaravone is low risk and circumvents the need for burdensome infusions, 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+**").

For patients who do not meet Study 19 criteria

The majority of ALS patients do not meet Study 19 inclusion criteria. In such patients, evidence from Study 16 and 18 does not show benefit for intravenous edaravone. Since oral edaravone is much less risky and burdensome than its intravenous counterpart, our certainty is too low to exclude a small net health benefit in other populations beyond Study 19. For patients who do not meet Study 19 criteria, we rate the evidence for oral edaravone added to standard of care compared to standard of care alone to be *insufficient* ("**I**").

Table 3.6. Evidence Ratings

Treatment	Population	Comparator	Evidence Rating
AMX0035	All ALS patients	Standard of Care	**C++**
Oral Edaravone	Meets narrow Study 19 criteria	Standard of Care	**C+**
Oral Edaravone	Does not meet Study 19 criteria	Standard of Care	**I**

4. Long-Term Cost Effectiveness

4.1. Methods Overview

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year.

The model evaluated hypothetical cohorts of patients with ALS. A single model was used for two separate analyses. The first analysis compared oral edaravone + SOC to SOC alone. SOC for the oral edaravone analysis was based on the comparator arm for the pivotal clinical trial for edaravone (Study 19) and included multidisciplinary care ± riluzole.[30] The second analysis compared AMX0035 + standard of care (SOC) to SOC alone. SOC for the AMX0035 analysis was based on the comparator arm for the pivotal AMX0035 clinical trial (CENTAUR) and included multidisciplinary care ± riluzole ± IV edaravone.[47]

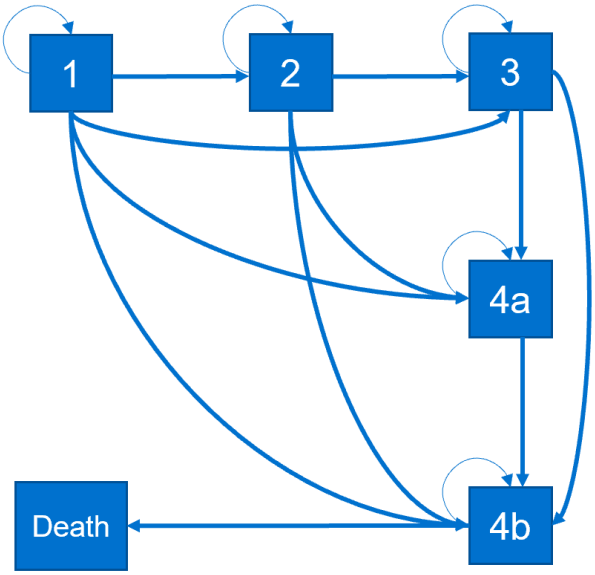
The model consisted of six health states, including death, which tracked the severity of disease, based on the King's ALS clinical staging system.[69] These health states included:

- Stage 1: functional involvement of one central nervous system (CNS) region (bulbar, arm, or leg)
- Stage 2: functional involvement of two CNS regions
- Stage 3: functional involvement of three CNS regions
- Stage 4a: functional involvement of at least one CNS region and the need for a feeding tube
- Stage 4b: functional involvement of at least one CNS region and the need for noninvasive ventilation (NIV)

In the King's staging system, forward progression from Stage 1 through Stage 3 is based on when patients indicate any loss of function on items related to bulbar, arm, or leg on the ALSFRS-R. Stages 4a and 4b are not sequential and Stage 4b overrides 4a if the need for a feeding tube and NIV both exist.

Figure 4.1 on the following page displays each of these health states and the possible transitions between each health state. In each subsequent cycle, patients can 1) stay in their health state 2) move forward by progressing to a worse health state or 3) die. Nonsequential transitions (e.g., Stage 1 to Stage 3) were possible in the model but no backward transitions are possible as patients progressively lose motor function. In both economic evaluations, patients remained in the model until death. All patients could transition to death from all causes from any of the alive health states. One month cycle lengths were used. Cost effectiveness was estimated using incremental cost-effectiveness ratios (cost per life year, QALY, and evLY gained).

Figure 4.1. Model Structure



4.2. Key Model Assumptions and Inputs

The King's staging system was used to model ALS progression because it has been widely used by the clinical community, has been used in a prior health technology assessment for edaravone,[70] has publicly available utilities measured for each health state based on a preferred instrument (EQ-5D)[35], and non-sequential jumps across health states depicting realistic clinical scenarios were possible.[71,72] These model assumptions and other modeling choices were informed by randomized clinical trials and open label extensions that provide the highest level of evidence given the heterogeneity of the patient population in relation to speed of progression.[30,47,48,63]

Our model includes several assumptions stated in Table 4.1.

Table 4.1. Key Model Assumptions

Model Choice or Assumption	Rationale
Oral edaravone's efficacy is the same as the IV form.	A study of oral edaravone showed bioequivalence to IV edaravone.[73]
The relative treatment effect of AMX0035 (25% relative risk reduction [RRR]) is constant across King's stages 1 through 4b.	The RRR was based on patients who started in King's stage 3, however there is no clear evidence to suggest a differential treatment effect in earlier stages.[47]
The relative treatment effect on progression of oral edaravone (hazard ratio [HR] of 0.665) is only applied to King's stage 1 through 3 and is constant across these stages.	In Study 16 and 18, which included patients with more progressed disease compared to Study 19, a significant treatment effect was not seen.
The proportion of patients who may receive treatment benefit of oral edaravone among all patients who receive treatment is 35%.	35% of patients from the broader Study 16 patient population met Study 19's inclusion criteria, which was based on treatment benefit.[48,58,74]
The relative disease progression treatment effects of both AMX0035 and oral edaravone are not the same for death. A separate relative mortality treatment effect for both interventions was informed by hazard ratios from survival analysis calibrated to observed clinical trial data.	In the open label extension studies for both interventions, a separate treatment effect on mortality was seen.[48,50]
A monthly treatment discontinuation probability was estimated from the 19% of AMX0035 patients and 1.4% of edaravone patients who discontinued treatment after six months.	These estimates are based on the CENTAUR and Study 19 clinical trials.[30,47]

IV: intravenous, RRR: relative risk reduction

Model inputs were identified from best available evidence and stakeholder engagement with clinicians and patients. The starting baseline distribution of patients in the model by King's stages was informed by patients' initial visit in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database that included 16 RCTs and one observational study.[75] The distribution was 21.8%, 28.0%, 25.1%, 21.4%, and 4.4% for King's stages 1, 2, 3, 4a, 4b, respectively. The primary clinical inputs included transition probabilities between the King's stages, treatment effects on disease progression and mortality, and treatment discontinuation. Monthly transition probabilities for patients on riluzole were calculated and served as the basis for which oral edaravone's and AMX's treatment effectiveness on progression and mortality were applied[72] based on EQ-5D responses from patients with ALS who participated in a large clinical trial.[35] The primary cost inputs included intervention drug costs, standard of care drug costs (IV edaravone and riluzole for AMX0035, riluzole for oral edaravone), and health state costs. For AMX0035, a placeholder price was used. For oral edaravone, the wholesale acquisition cost (WAC) was used in the model as information on price discounts were not known, and similar costs between WAC and the average sales price (ASP)

were seen for the IV formulation. Future reports may use a different price point as updated information becomes available. Select model inputs are found in Table 4.2 and a detailed description of each model input that informed the model can be found in Supplement Section E2.

Table 4.2. Key Model Inputs

Parameter	Value	Source	Notes
Oral edaravone HR on disease progression	0.665	Study 19 and CADTH pharmacoeconomic report[30,70]	Applied to King's stages 1 through 3; calculated from RRR of progression of 25% and the annual rate of disease progression assuming a constant hazard. Only applied to 35% of the treated population.
Oral edaravone HR on mortality	1.0	Open label extension study[63]	Applied to all transitions from King's stages 1 through 4b to death
AMX0035 RRR on disease progression	0.75	CENTAUR trial[47]	Calculated from relative monthly change in decline on ALSFRS-R survey
AMX HR on mortality	0.74	Calibrated from HR noted in FDA AdComm Meeting [49]	The HR on mortality was calibrated in the model to match the median overall survival difference of 4.8 months observed in the survival results presented at the FDA AdComm Meeting.
Probability (monthly) of treatment discontinuation	Oral Edaravone: 0.23% AMX0035: 3.47%	Study 19 and CENTAUR trial[25,71]	Calculated as a monthly probability from the discontinuation rates at six months
Patient utilities (according to King's stages)	Stage 1: 0.65 Stage 2: 0.53 Stage 3: 0.41 Stage 4a & 4b: 0.27	Jones AR et al. 2014[35]	Provided by persons with ALS in the UK who participated in a clinical trial using the ED-5D
Oral edaravone annual cost	$171,000	Redbook	Wholesale acquisition cost
AMX0035 annual cost	$169,000	Placeholder price (assumption)	Based on annual parity price to IV edaravone

4.3. Results

Conventional Base-Case Results

The draft report results may change as we continue to receive stakeholder feedback on model inputs and assumptions. The total discounted costs, QALYs, evLYs, and life years are detailed in Table 4.3 for oral edaravone + SOC versus SOC alone. Over the lifetime time horizon, treatment with oral edaravone in addition to SOC resulted in incremental costs of approximately $432,000, and incremental QALYs and evLYs of approximately 0.04 and 0.05, respectively, compared to SOC alone from the health care sector perspective. The modest survival benefit from the conventional base-case analysis with oral edaravone compared to SOC is optimistic and a result of delaying progression in the model using a patient's lifetime time horizon. A more detailed summary of the costs is in the supplement.

Table 4.3. Results for the Conventional Base-Case for Oral Edaravone plus Standard of Care (Multidisciplinary Care ± Riluzole) Compared to Standard of Care alone, Health Care Sector Perspective

Treatment	Drug Cost	Total Cost	QALYs	evLYs	Life Years
Oral Edaravone + SOC (Multidisciplinary Care ± Riluzole)	$428,000	$598,000	0.93	0.94	2.70
SOC alone	$1,300	$166,000	0.89	0.89	2.64

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year, SOC: standard of care

The total discounted costs, QALYs, evLYs, and life years, using a placeholder price for AMX0035 equal to that of IV edaravone, are detailed in Table 4.4 for AMX0035. Over the lifetime time horizon, treatment with AMX0035 in addition to SOC resulted in incremental costs of approximately $299,000 and incremental QALYs and evLYs of approximately 0.14 and 0.31, respectively, from the health care sector perspective. A more detailed summary of the costs is in the Supplement.

Table 4.4. Results for the Conventional Base-Case for AMX0035 plus Standard of Care (Multidisciplinary Care ± Riluzole ± IV Edaravone) Compared to Standard of Care alone, Health Care Sector Perspective

Treatment	Drug Cost	Total Cost	QALYs	evLYs	Life Years
AMX0035 + SOC (Multidisciplinary Care ± Riluzole ± IV Edaravone)	$379,000*	$569,000*	1.03	1.21	3.01
SOC alone	$105,000	$270,000	0.89	0.89	2.64

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year, SOC: standard of care
*based on placeholder price

Table 4.5 presents the incremental cost-effectiveness ratios from the conventional base-case analysis, which includes estimates for the incremental cost per QALY gained, incremental cost per evLY gained, and incremental cost per life year gained. For oral edaravone in addition to SOC compared to SOC alone, the incremental cost per QALY gained was approximately $11.99 million from the health care system perspective, and the incremental cost per evLY gained was approximately $8.19 million. For AMX0035 in addition to SOC compared to SOC alone, the incremental cost per QALY gained was approximately $2.14 million from the health care system perspective, while the incremental cost per evLY gained was approximately $0.95 million.

Table 4.5. Incremental Cost-Effectiveness Ratios for the Conventional Base Case, Health Care Sector Perspective

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Oral Edaravone + SOC (Multidisciplinary Care ± Riluzole)	SOC alone	$11,986,000	$8,195,000	$6,983,000
AMX0035 + SOC (Multidisciplinary Care ± Riluzole ± IV Edaravone)	SOC alone	$2,136,000*	$952,000*	$810,000*

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year, SOC: standard of care
*based on placeholder price

Sensitivity Analyses

Results from one-way sensitivity analyses and probabilistic sensitivity analyses for both oral edaravone and AMX0035 can be found in Supplement Section E4. Of note, the incremental cost-effectiveness ratios were not sensitive to patient utilities according to King's Stage. The most influential factors included treatment effectiveness and presumed cost of the interventions.

Scenario Analyses

We conducted numerous scenario analyses to examine uncertainty and potential variation in the findings. We list the various scenarios below and present the findings for Scenarios 1 and 8 in Table 4.6. The remaining scenarios are detailed in Supplement Section E5.

- Scenario Analysis 1: Modified societal perspective
- Scenario Analysis 2: Assuming patients discontinue treatment once they progress to King's Stage 4a and 4b
- Scenario Analysis 3: Assuming all persons diagnosed with ALS enter the model at King's Stage 1 and receive treatment immediately

- Scenario Analysis 4: Assuming the treatment effect (HR=0.665) from oral edaravone continues throughout King's Stage 4a and 4b
- Scenario Analysis 5: Assuming all patients who take oral edaravone receive treatment benefit
- Scenario Analysis 6: Assuming AMX0035 does not have a separate survival benefit
- Scenario Analysis 7: Assuming IV edaravone is not part of the standard of care therapy used for patients using AMX0035
- ICER Reference Case Scenario Analysis: In certain situations where standard of care costs are high, interventions that extend life do not have plausible value-based prices according to standard methods. Consistent with ICER's Reference Case for such situations, we conducted an analysis that removed the non-drug health care and standard of care drug costs. This analysis may be useful for policy maker deliberations on value-based prices.

Table 4.6. Scenario Analysis Results

Scenario 1: Modified Societal perspective	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$12,190,000	$8,335,000	$7,102,000
	AMX0035 + SOC†	SOC† alone	$2,435,000‡	$1,085,000‡	$924,000‡
ICER Reference Case Analysis: Assuming $0 health state and SOC drug costs	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$11,833,000	$8,090,000	$6,894,000
	AMX0035 + SOC†	SOC† alone	$1,858,000‡	$828,000‡	$705,000‡

evLY: equal value of life-year, IV: intravenous, QALY: quality-adjusted life-year, SOC: standard of care

* Multidisciplinary Care ± Riluzole

† Multidisciplinary Care ± Riluzole ± IV Edaravone

‡ Based on placeholder price

Threshold Analyses

Threshold analyses were conducted to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds. For both interventions, given the high cost of background care, we conducted threshold analyses with health state and SOC drug costs included based on the QALY (Table 4.7) and the evLY (Table 4.8), and with health state and SOC drugs costs excluded based on the QALY (Table 4.9) and the evLY (Table 4.10).

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

Drug/Treatment	Annual Price	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Oral Edaravone	$171,000	NA	NA	NA	$687
AMX0035	$169,000*	NA	NA	NA	NA

QALY: quality-adjusted life-year, NA: not available

*Based on placeholder price

Table 4.8. evLY-Based Threshold Analysis Results with Health State and Standard of Care Drug Costs Included

Drug/Treatment	Annual Price	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Oral Edaravone	$171,000	NA	NA	$1,000	$2,000
AMX0035	$169,000*	NA	NA	$5,300	$15,500

evLY: equal value life-year, NA: not available

*Based on placeholder price

Table 4.9. QALY-Based Threshold Analysis Results with Health State and Standard of Care Drug Costs Excluded

Drug/Treatment	Annual Price	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Oral Edaravone	$171,000	$700	$1,400	$2,200	$2,900
AMX0035	$169,000*	$4,500	$9,100	$13,700	$18,200

QALY: quality-adjusted life-year

*Based on placeholder price

Table 4.10. evLY-Based Threshold Analysis Results with Health State and Standard of Care Drug Costs Excluded

Drug/Treatment	Annual Price	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Oral Edaravone	$171,000	$1,100	$2,100	$3,200	$4,200
AMX0035	$169,000*	$10,200	$20,400	$30,600	$40,800

evLY: equal value life-year
*Based on placeholder price

Uncertainty and Controversies

There were important uncertainties relevant to generating model outcomes, most of which related to the effectiveness on disease progression and mortality for both oral edaravone and AMX0035. As emphasized in the comparative effectiveness section of this report, the evidence on the effectiveness of AMX0035 is limited to one RCT with a relatively small sample size. While AMX0035 did show a significant reduction in decline in the ALSFRS-R score, its effectiveness is modest, especially when using more appropriate statistical methods. Furthermore, given methodological concerns with the CENTAUR trial (i.e., randomization implementation error) and no survival benefit seen during the randomization phase, along with the fact that no other RCTs or observational studies have assessed AMX0035's effect on mortality, we remain uncertain as to whether the hazard ratio used in the model represents the true survival benefit of AMX0035.

Similarly, the robustness of the evidence on oral edaravone's treatment effect is limited. Earlier RCTs (i.e., Study 16, Study 18) did not slow disease progression for patients who added edaravone to their SOC. The significant results for edaravone came from Study 19, which consisted of a narrow subset of ALS patients from Study 16 that showed potential benefit in receiving intravenous edaravone. The impact of edaravone on survival is more uncertain as the entirety of Study 19, including the open label extension, only had three deaths across both treatment arms.[63] One observational study also did not show a survival benefit.[57] A survival benefit from oral edaravone is seen in the model due to its effects on progression. Given the study results above, this may be optimistic. Additional uncertainties regarding the treatment effectiveness for both oral edaravone and AMX0035 include not knowing whether the treatment effect on progression is consistent across King's stages 1-3 and King's stages 1-4b, respectively. Furthermore, the cost-effectiveness model would be more accurate if the mix of patients with heterogenous rate of disease progression could be taken into account. While clinical experts in ALS agree that there are differential rates in progression as well as treatment effect by King's stage, these data are currently unavailable to incorporate into the model.

4.4 Summary and Comment

The incremental cost effectiveness of oral edaravone, assuming the same effectiveness as IV edaravone, far exceeds typical cost-effectiveness thresholds. This finding held across a wide range of scenario and sensitivity analyses and is the case in analyses using cost per evLY gained, which value any life extension as if it occurred with normal health.

Assuming a placeholder price for AMX0035 equal to that of IV edaravone, it too would have an incremental cost effectiveness that far exceeds typical cost-effectiveness thresholds, however its cost effectiveness is superior to that of edaravone because of the modeled prolongation in survival as observed in the CENTAUR OLE. As discussed in the clinical section, we have uncertainties about this survival benefit. Ultimately, the cost effectiveness of AMX0035 will depend on its price and confirmation of its clinical benefits.

5. Contextual Considerations and Potential Other Benefits

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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	The acuity of need for an effective treatment is extremely high as in most patients ALS is a rapidly progressive disease leading to worsening disability and then death over a short period of time.
Magnitude of the lifetime impact on individual patients of the condition being treated	For most patients, ALS occurs in later adulthood. While ALS affects only a portion of an individual's lifespan, the impact during that affected time is large.
New mechanism of action may provide benefit to patients	ALS is a heterogenous illness with multiple cellular pathways to neuronal death. Having more than one therapeutic option that disrupts different pathways may offer more options. However, the mechanism of action for both AMX0035 and edaravone are uncertain.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	For most patients, ALS occurs at an older age where many of these major life goals will not be affected. Delaying progression of ALS may affect the latter stages of careers and could have a significant impact on family life.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Caregiving for patients with ALS can require many hours per week and also create financial toxicity. As such, particularly for younger family members, caregiving for ALS can interfere with the ability to achieve major life goals. Benefits on younger caregivers of an effective therapy may not be adequately captured in cost-effectiveness analyses.
Patients' ability to manage and sustain treatment given the complexity of regimen	Intravenous edaravone is so burdensome and risky that many clinicians do not recommend it and many patients choose not to take it. Oral edaravone has major advantages in terms of reducing this burden and allowing access to treatment with edaravone.
Society's goal of reducing health inequities	AMX0035 and oral edaravone would provide more treatment options. However, potential reduction in health inequities may be tempered by high out-of-pocket costs among underinsured individuals, who are more likely to be racial/ethnic minorities.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness analyses were used to estimate the total potential budget impact of oral edaravone + SOC compared to SOC alone, and separately for the impact of AMX0035 + SOC versus SOC alone. For AMX0035, we used a placeholder annual price equal to that of IV edaravone, and for both oral edaravone and AMX0035 we used threshold prices at $50,000, $100,000, and $150,000 per QALY in our estimates of budget impact. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs are undiscounted and estimated over a five-year time horizon.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we applied a prevalence estimate of 24,800,[2,9] incidence estimates (2 per 100,000 individuals),[8] and a death rate of 7,000 individuals per year to the 2022-2026 projected US population. Applying these sources resulted in an average estimated prevalence of 24,353 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 4,871 patients per year. Given we are assessing two new market entrants, we assumed that 50% of patients each year (N = 2,435) will initiate AMX0035 (added on to standard of care, i.e., riluzole ± edaravone ± multidisciplinary care) and the remaining 50% of patients each year (N = 2,435) will initiate oral edaravone (added on to standard of care, i.e., riluzole ± multidisciplinary care). We recognize that there may be other combinations of agents used in clinical practice, however, our analysis focused on those modeled in the cost-effectiveness analysis.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplement Section F.

7.2. Results

Figure 7.1 illustrates the cumulative per patient potential budget impact for oral edaravone + SOC compared to SOC alone. The average annual budget impact per patient was $155,556 in year one

with cumulative net annual costs increasing to $399,918 in year five. Annual net costs decreased in years two through five due to treatment discontinuation and the average life expectancy of persons with ALS being between two to five years. 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. At prices to reach thresholds of $150,000, $100,000, and $50,000 per QALY, 100% of patients could be treated over five years before reaching the ICER potential budget impact threshold of $734 million per year.

Figure 7.1. Cumulative Net Cost per Patient Treated with Oral Edaravone

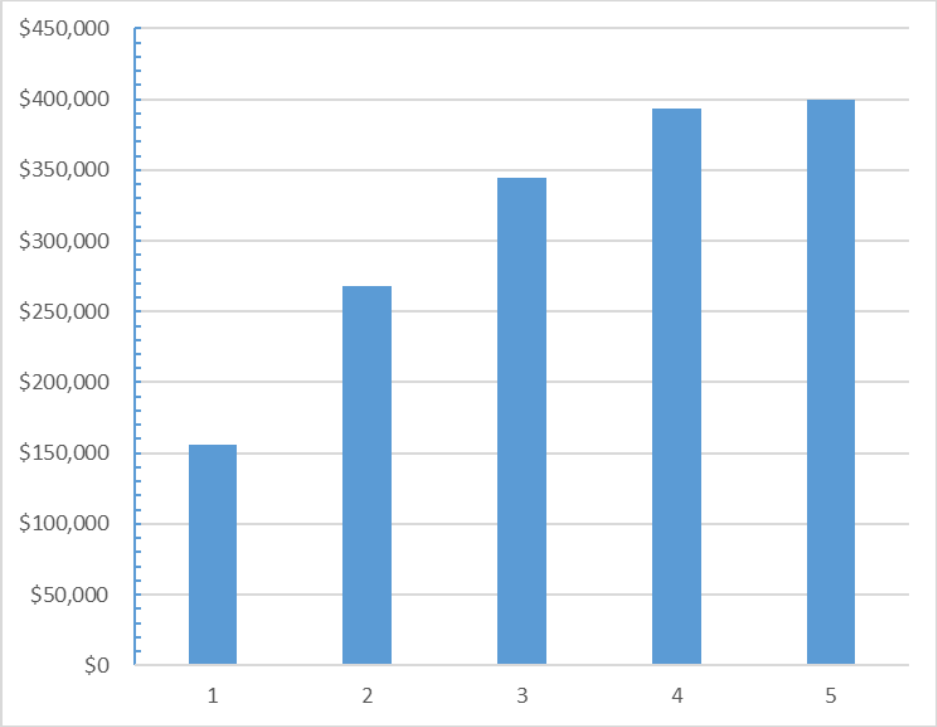
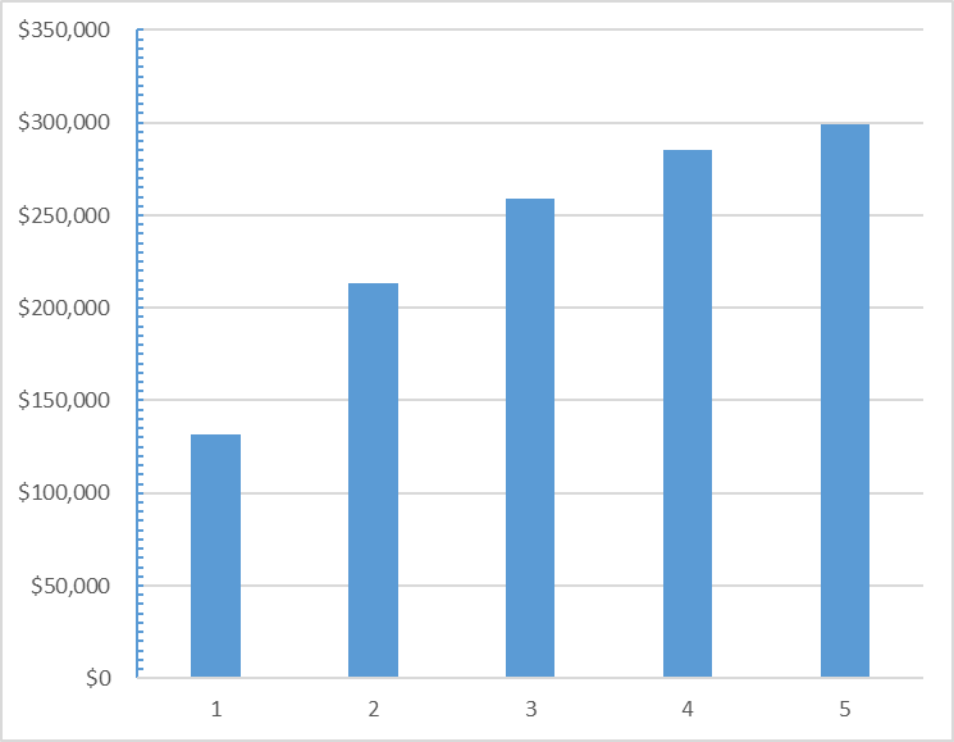


Figure 7.2 illustrates the cumulative per patient potential budget impact for AMX0035 compared to SOC, based on a placeholder price equal to that of IV edaravone. The average annual budget impact per patient was $131,994 in year one with cumulative net annual costs increasing to $266,396 in year five. Annual net costs decreased in years two through five due to treatment discontinuation and the average life expectancy of persons with ALS being between two to five years. 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. Likewise, at prices to reach thresholds of $150,000, $100,000, and $50,000 per QALY, all patients could be treated over five years before reaching the ICER potential budget impact threshold of $734 million per year.

Figure 7.2. Cumulative Net Cost per Patient Treated with AMX00035 at Placeholder Price



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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Amyotrophic Lateral Sclerosis (ALS): a rare, progressive, neurodegenerative disease characterized by loss of motor neurons in the brain and spinal cord. There is great heterogeneity in clinical presentation based on which motor neurons are affected. ALS commonly begins with localized weakness and progresses to affect most muscles. After symptom onset, people with ALS often die within three to five years from respiratory muscle paralysis.[1]

- **Sporadic ALS:** occurring without a family history and accounts for approximately 90% of people with ALS.
- **Familial ALS:** known ALS history within a family and accounts for approximately 10% of people with ALS.
- **Bulbar Onset ALS:** symptoms first present in the face or neck such as difficulty chewing or swallowing.
- **Limb Onset ALS:** symptoms first present in the limbs such as muscle cramps, stiffness, or muscle twitching.

Accurate Test of Limb Isometric Strength (ATLIS) Score: a measure of muscle strength using a device that measures the isometric strength of 12 muscle groups in the arms and legs. The ATLIS has three components including total ATLIS, upper extremity ATLIS, and lower extremity ATLIS.[76]

Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R): a validated measure commonly used in ALS care settings and clinical trials to measure a person's function and ability to maintain daily activities**.** The measure uses an ordinal rating scale ranging from zero to four for 12 individual functional activities within four functional categories: bulbar, breathing, fine motor, and gross motor. The maximum score is 48 points, with a higher score indicating better function.[49] The table below outlines the individual categories.

Table A1. ALSFRS-R Components

Domain	Item
Bulbar	Speech
	Salivation
	Swallowing
Fine Motor	Handwriting
	Cutting Food
	Dressing and Hygiene
Gross Motor	Turning in bed
	Walking
	Climbing Stairs
Respiratory	Dyspnea
	Orthopnea
	Respiratory Insufficiency

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised

El Escorial Revised Airlie House Diagnostic Criteria: This diagnostic criteria has evolved over time and classifies patients with ALS into categories reflecting different levels of diagnostic certainty, based on evidence of both lower and upper motor neuron degeneration, progressive spread of symptoms, and absence of other pathological or neuroimaging evidence that may influence the motor neuron degeneration or other signs of ALS. There are several categories of diagnostic certainty, including definite ALS, probable ALS, probable ALS (laboratory results supported), and possible ALS.[77]

Forced (FVC) and Slow Vital Capacity (SVC): These are measures of respiratory function in people with ALS. FVC is the total amount of air able to be forcibly exhaled from an individual's lung after taking a deep breath during the forced expiratory volume (FEV) respiratory test. Alternatively, SVC uses an unforced technique to measure the volume of air exhaled.[78]

Japanese ALS Severity Classification: a classification staging scale to assess ALS severity, ranging from one to five, with a lower stage indicating better functioning. The stages are defined as: "(1) able to work or perform housework; (2) independent living but unable to work; (3) requiring assistance for eating, excretion or ambulation; (4) presences of respiratory insufficiency, difficulty in coughing out sputum or dysphagia; (5) using a tracheostomy tube, tube feeding, or tracheostomy positive pressure ventilation."[32]

Modified Norris Scale: a scale for rating function in people with ALS with two components, limb and bulbar. The limb score has 21 items rated on an ordinal scale from zero to four with a maximum score of 63. The bulbar score has 13 items rated on an ordinal scale from zero to four with a maximum score of 39.[79]

Phosphorylated neurofilament heavy chain protein (pNF-H): a biomarker in the CSF and plasma that is postulated to increase as a result of motor axon breakdown and degeneration as ALS

progresses. The plasma pNF-H biomarker is not validated and was included as an exploratory secondary endpoint in the CENTAUR trial.[80]

Tracheostomy: a surgical procedure to allow for the use of a ventilator to permanently aid in an individual's breathing often used to increase oxygen levels or reduce shortness of breath.[81]

Permanent Assisted Ventilation (PAV): clinical outcome in CENTAUR clinical trial defined as more than 22 hours daily of non-invasive ventilation for more than one week.[47]

A2. Potential Cost-Saving Measures in ALS

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for ALS, such as the 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. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with ALS that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's scoping, open input, and public comment periods, we received public comment submissions from seven stakeholders (two patient advocacy groups, four manufacturers, and one individual) and participated in conversations with fourteen key informants (seven clinicians, two patient advocacy groups (The ALS Association and I AM ALS), two individuals living with ALS, two manufacturers, and one payer). Organized by I AM ALS, we also conducted a focus group with 12-15 participants who were either people with ALS or current or former caregivers. The feedback received from written input and scoping conversations helped us to understand and discuss the impact of ALS on patients and caregivers described in section two of the draft evidence report.

C. Clinical Guidelines

Clinical practice guidelines for the treatment of ALS have been issued by one US and several non-US-based professional and society organizations. These guidelines are summarized below.

American Academy of Neurology[23]

In 2009, the American Academy of Neurology (AAN) published an update to their practice parameter guideline on the care of patients living with ALS, which issued recommendations for drug, nutritional and respiratory therapies.

1. ***Drugs***: AAN recommended the use of riluzole to slow disease progression in patients with ALS (level A recommendation). Specifically, the level A recommendation applied to treating patients with definite or probable ALS, FVC greater than 60%, and absence of a tracheostomy. The AAN committee's expert opinion suggested potential benefit for those with suspected or possible ALS with symptoms longer than five years, FVC less than 60%, and tracheostomy (for prevention of aspiration only). Of note, this guideline was reaffirmed January 11, 2020, and does not discuss or make a recommendation for edaravone, which was approved by the FDA in 2017.

2. ***Nutrition***: Changing food consistency and using nutritional supplements were recommended as strategies to maintain nutritional intake. When feeding and maintaining caloric intake becomes difficult, supplemental enteral nutrition through a percutaneous endoscopic gastronomy (PEG) or equivalent device should be considered given their likely benefit to stabilize body weight and to prolong survival (Level B). There was insufficient evidence regarding the most optimal time for inserting a PEG to start enteral nutrition (Level U), although a single low-quality study suggested lower risks of PEG when FVC is above 50%. The AAN recommended against the use of two nutritional supplements to improve quality of life or survival: creatine (Level A) and high-dose Vitamin E (Level B).

3. ***Respiratory management:*** Because most ALS patients will die from respiratory failure, timely diagnosis and management is important. FVC in the erect position is the most commonly used measurement of respiratory capacity in ALS but may be insensitive to detect early respiratory insufficiency. Supported by low-quality evidence, the AAN recommended to consider the use of nocturnal oximetry to detect hypoventilation irrespective of the FVC (Level C), and to consider the use of FVC in the supine position and maximal inspiratory pressure (MIP) in addition to erect FVC for routine respiratory monitoring (Level C). Regarding management, recommendations were made to consider non-invasive ventilation, as well as invasive ventilation via a tracheostomy if long-term ventilation is desired, which can potentially improve quality of life in people with respiratory insufficiency (Level C).

European Federation of Neurological Societies[82]

In 2012, the European Federation of Neurological Societies (EFNS) task force convened to create a revised report for the diagnosis and management of ALS. Based on expert consensus, the guideline recommended to make a diagnosis of ALS as early as possible, in part to initiate treatment with neuroprotective drugs when fewer cells might be affected. Similar to AAN, the EFNS guideline also recommended riluzole as the only disease-modifying treatment for ALS (Level A) and non-invasive ventilation to prolong survival (Level A) and improve quality of life (Level C). Unlike AAN, EFNS make recommendations for multidisciplinary care to possibly extend survival, decrease medical complications (Level B), and improve quality of life (Level C), as well as several recommendations for symptomatic management. These include antidepressants (Level B) and a combination of dextromethorphan and quinidine (Level C) for pseudobulbar emotional lability, modafinil for debilitating fatigue (Level A), and botulin toxin injections for refractory sialorrhea (Level B).

Canadian ALS Research Network Guideline[83]

In 2020, experts within the Canadian ALS Research Network (CALS) issued a guideline providing best practice recommendations for the management of people living with ALS in Canada. Similar to the AAN and EFNS guidelines, the Canadian guideline placed emphasis on the management of ALS through multidisciplinary care (Level B), enteral feeding tube insertion (Level C), and noninvasive ventilation (Level B). Regarding pharmacologic therapies, in addition to riluzole (Level A), the Canadian guideline is the only major guideline to recommend the use of intravenous edaravone, but only in the very select population that met Study 19 inclusion criteria (Level B recommendation), which includes: disease duration < 2 years, FVC > 80%, all ALSFRS-R item scores > 2 and demonstrated steady decline in the ALSFRS-R over a 3-month preceding interval. Based on expert consensus, intravenous edaravone was not recommended to slow disease progression for other stages or patients beyond the Study 19 inclusion criteria.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

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 intravenous edaravone. We do not anticipate comparing the net clinical benefit between AMX0035 and edaravone.

Comparators

We plan to compare 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.

Table D1. PRISMA 2020 Checklist[84]

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.

	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on AMX0035 and oral edaravone for ALS followed established best research methods.[85,86] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[84] The PRISMA guidelines include a checklist of 27 items.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

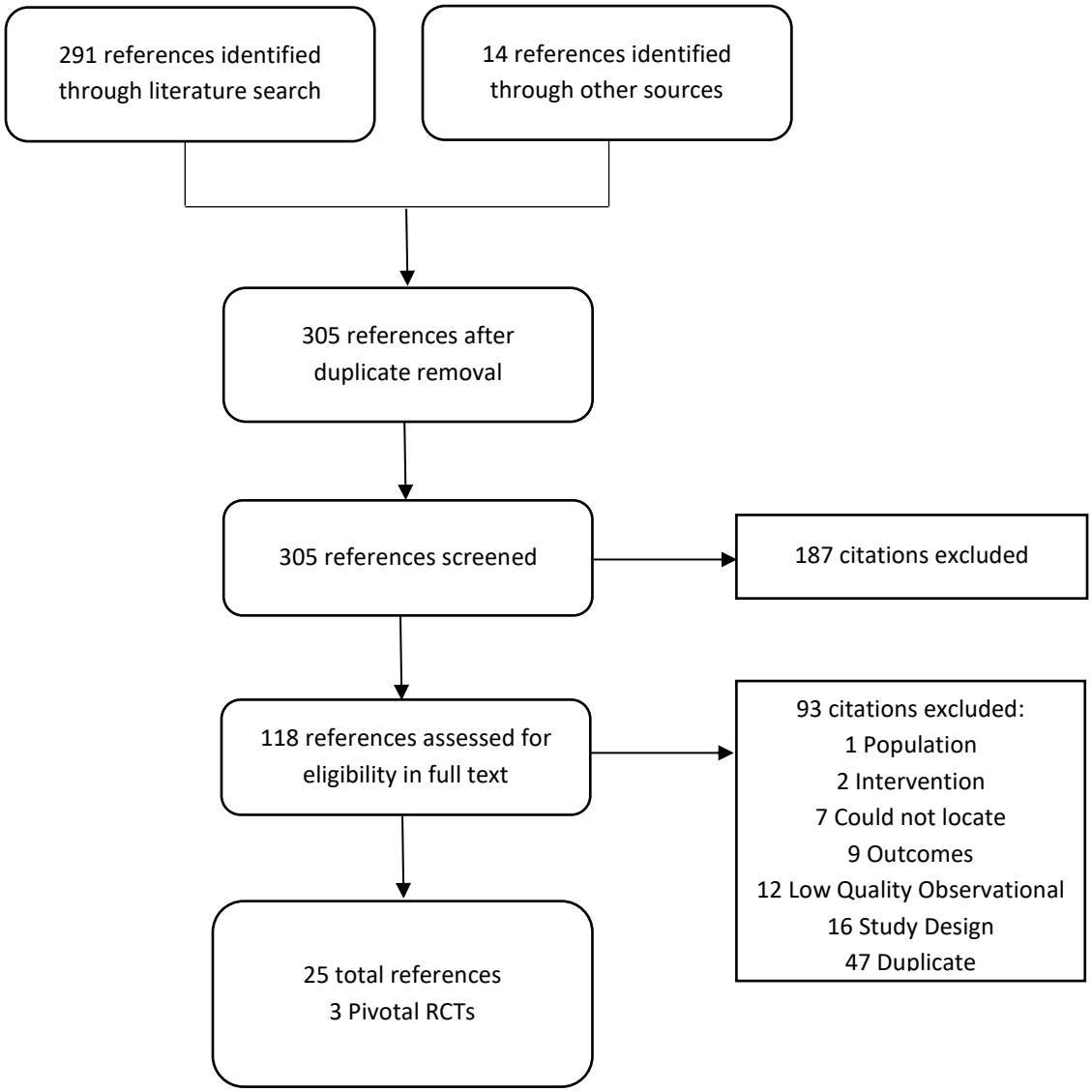
Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp motor neuron disease/ OR exp amyotrophic lateral sclerosis/
2	(motor neuron disease OR amyotrophic lateral sclerosis OR ALS).ti,ab OR (lou Gehrig* AND (disease* OR syndrome*)).ti,ab
3	1 OR 2
4	(AMX0035 OR AMX 0035).ti,ab OR (sodium phenylbutyrate-taurursodiol).ti,ab OR (TUDCA OR TURSO OR taurursodiol OR sodium phenylbutyrate).ti,ab
5	Edaravone/ OR (edaravone OR radicava OR radicut OR xavron OR MCI186 OR MCI 186 OR MCI-186 OR oral edaravone OR MT1186 OR MT-1186 OR MT 1186).ti,ab
6	4 OR 5
7	3 AND 6
8	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
9	(animals not (humans and animals)).sh.
10	8 OR 9
11	7 NOT 10
12	Limit 11 to English Language

Table D3. Search Strategy of EMBASE SEARCH

1	‘motor neuron disease'
2	('moto* neuron* disease*' or 'moto?neuron* disease')
3	amyotrophic lateral sclerosis OR 'ALS' OR (lou AND gehrig* and disease* or syndrome*)
4	1 OR 2 OR 3
5	‘edaravone' OR 'radicava' OR 'MT-1186' OR 'radicut' OR 'xavron' OR 'MCI186' OR 'MCI*186' OR 'MTI186' OR 'MTI*186'
6	‘AMX0035' OR 'AMX*35' OR 'PB and TURSO' OR ('sodium phenylbutyrate' AND 'taurursodiol')
7	4 AND 5
8	4 AND 6
9	7 OR 8
10	('case report'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
11	#9 NOT #10
12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
13	#11 NOT #12
14	#13 AND [english]/lim

Figure D1. PRISMA flow Chart Showing Results of Literature Search for AMX0035 and Edaravone



Study Selection

We performed screening at both the abstract and full-text levels. Two investigators independently screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. One investigator reviewed full papers and provided justification for the exclusion of each excluded study.

We also included FDA documents related to AMX0035 and edaravone. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[87] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[88,89]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for AMX0035 and edaravone using clinicaltrials.gov. Search terms included "AMX0035," "Intravenous edaravone," "IV edaravone," "oral edaravone," "Radicava,", "MCI186," "MT1186," "ALS," and "amyotrophic lateral sclerosis."

We did not identify any studies for AMX0035, intravenous edaravone, or oral edaravone that would have met our inclusion criteria and for which no findings have been published within two years.

Data Synthesis and Statistical Analyses

Relative data on key outcomes of the main studies were summarized in evidence tables (see Section D3 below) and synthesized qualitatively and quantitatively in the body of the report. Key differences between studies (study design, patient characteristics, interventions, outcomes, study quality) were explored in the text of the report. We assessed the feasibility of quantitative synthesis and due to differences in the trials as well as standard of care in patients with ALS, we did not conduct a meta-analysis or network meta-analysis to compare AMX0035 and edaravone.

D2. Additional Clinical Evidence

Evidence Base

AMX0035

CENTAUR

A total of 137 patients from 25 treatment centers across the Northeast Amyotrophic Lateral Sclerosis consortium (NEALS) were randomized in a 2:1 ratio to treatment (n= 89) and placebo (n= 48). Patients in the treatment arm received a combined powdered oral formulation sachet of 3 grams (PB) and 1 gram of (TURSO) once a day for three weeks, and then up to twice daily (one sachet twice a day) thereafter. To be included in CENTAUR, patients had to be diagnosed with sporadic or familial ALS, with a symptom onset of 18-months or less, SVC greater than 60% and were allowed to be naïve, or on a stable dose of riluzole for at least 30 days.[47] Patients were allowed to initiate edaravone during the study, which was approved by the FDA after the start of the CENTAUR trial.[48] Overall, at baseline the mITT population had an average ALSFRS-R score of 36, an average ALS duration of six months since diagnosis, and 27% had bulbar-onset ALS. The average age of participants in the trial was 58 years, with most participants in the trial identifying as male (69%) and white (95%).[47]

The primary efficacy endpoint of the CENTAUR trial was the rate of decline in the ALSFRS-R total score at the end of the 24 weeks using a linear mixed model assumption adjusting for age and pre-baseline ALSFRS-R slope.[47] Secondary outcomes included rate of decline in isometric muscle strength assessed by ATLIS; respiratory function assessed by SVC; and the plasma phosphorylated neurofilament heavy chain H subunit levels (pNF-H) biomarker. The minimal clinical important difference (MCID) is not established for any of these secondary outcomes in ALS.

The main secondary outcome related to survival is a composite of time to death, tracheostomy, or permanent ventilation. The results of the primary efficacy endpoint are reported in the main section of the report. All secondary outcomes from CENTAUR—which include ATLIS, SVC, pNF-H biomarker, time to death, tracheostomy or PAV, death alone, and hospitalizations—are reported below. Data from CENTAUR is supplemented by the FDA briefing document and slide presentations from the FDA Advisory Committee Meeting.[49-51]

CENTAUR-OLE

Patients were eligible to enter the OLE if they completed all visits required during the CENTAUR trial. Among the 89 patients in the treatment arm of the CENTAUR trial, 60 patients (67%) completed the study during the randomized phase. Of 48 participants randomized to the placebo arm, 37 patients (77%) completed the study. Of the 98 patients from the CENTAUR trial that were

eligible to enter the OLE, 90 participants (92%) enrolled, including 56 from the original treatment arm and 34 from the original placebo arm of the CENTAUR trial.[47]

As mentioned in the main section of our report, the survival outcome for the OLE publication was time to death, based on all-cause mortality, between participants originally randomized to treatment or placebo using an ITT approach. This was assessed by calculating the median duration of survival using a Kaplan-Meier curve and Cox proportional model to estimate the hazard ratio, adjusting for age at randomization, pre-baseline ALSFRS-R slope and baseline ALSFRS-R total score. Other survival related endpoints include time to first hospitalization and time to death or death equivalent events (tracheostomy or PAV). Survival probabilities were calculated at 12 months and 24 months.[48] These time-to-event endpoints for the OLE are reported based on the most recent cut-off date of March 1, 2021.

Oral Edaravone

Across the MCI-186 trial program of intravenous edaravone, there were several similarities in study design and inclusion criteria. Eligible trial participants were required to have 'normal' respiratory function, as indicated by a score of 4 on the ALSFRS-R subdomains of dyspnea, orthopnea, and respiratory insufficiency. The full inclusion criteria of each trial are outlined in Table D4. Each trial had a duration of 24 weeks for efficacy plus a 12-week pre-observation period before randomization. To ensure a measurable treatment effect, eligible patients were required to have a decrease in the ALSFRS-R score of 1 to 4 points during the pre-observation period. All participants received infusions of edaravone 60mg or matching placebo in six, four-week cycles. The initial treatment cycle involved treatment for 14 consecutive days with a 14-day observation period; subsequent cycles (cycles 2-6) required treatment for 10 of the 14 days followed by another 14-day observation period. The primary efficacy endpoint in all three MCI-186 trials was change in ALSFRS-R score over a 24-week treatment period. The secondary endpoints were change in FVC (%), total Modified Norris Scale score, ALS severity classification, grip and pinch strength (kg), total ALSAQ-40 score, and time to death or specified state of disease progression (defined as disability of independent ambulation, loss of upper-limb function, tracheostomy, use of a respirator, use of tube feeding, or loss of useful speech). The minimal clinically important difference (MCID) is not established for any of these secondary outcomes in ALS.

Table D4. Inclusion Criteria of MCI-186 Clinical Development Program[30-32,47,74]

	Study 16		Study 19	Study 18
	FAS	Post-Hoc dpEESP2y	FAS	FAS
Japan ALS severity classification	Grade 1 or 2			Grade 3
Measure of respiratory function	4 points on ALSFRS-R items of dyspnea, orthopnea, and respiratory insufficiency			
Change during pre-observation period	Change in ALSFRS-R score of -1 to -4 points			
Baseline ALSFRS-R score	Not specified	≥2 points on all 12 items of ALSFRS-R		Not specified
Respiratory Function	FVC ≥ 70%	FVC ≥ 80%		FVC ≥ 60%
El Escorial revised Airlie House diagnostic criteria	Definite, probable, probably laboratory-supported	Definite or probable		Definite, probable, probably laboratory-supported
Onset of ALS	≤ 3 years	≤ 2 years		≤ 3 years

ALS: amyotrophic lateral sclerosis, ALSFRS-R: amyotrophic lateral sclerosis functional rating score-revised, DB: double blind, E: edaravone, FAS: full analysis set, FVC: forced vital capacity

Witzel et al. was an observational multicenter cohort study that evaluated the effectiveness and safety of intravenous edaravone as an add-on therapy to standard therapy of riluzole versus riluzole alone. Effectiveness was assessed among patients cared for in one of 12 German multidisciplinary ALS centers who received at least four treatment cycles of edaravone (as-treated analysis), which followed the dosing regimen of the MCI-186 clinical trial program. Study participants were propensity-score matched using nearest-neighbor 1:1 matching with a caliper of 0.2 for three covariates (age at onset, disease duration, and baseline ALSFRS-R score), and exact matching for site of disease-onset. The propensity-score matched sample for survival analysis included 130 patients treated with edaravone and 130 concurrent matched controls. At baseline among the 130 matched-patients in the edaravone group, the median age was 57.5 years, median disease duration was 16.4 months, the median ALSFRS-R score was 38, the monthly median decline of the ALSFRS-R score was -0.58 points, and 97% were on riluzole treatment. The disease progression analysis included 116 patients in each arm.

SUNRISE Japan is an ongoing 5-year post-marketing surveillance study that is evaluating the real-world efficacy and safety of intravenous edaravone. Ishizaki et al. reported the incidence of adverse drug reactions of 800 edaravone-treated Japanese patients with up to one year of follow-up. At baseline, patients had a mean ALSFRS-R score of 38.5 and a mean FVC of 83.6%.

MT-1186-A01 is an ongoing open-label multicenter international Phase 3 trial seeks to evaluate the safety and tolerability of oral edaravone. Adults within three years of their first ALS-related

symptom who were living independently and had a minimum baseline FVC of 70% were eligible for treatment. 185 enrolled participants across North America, western Europe, and Japan were treated with 105mg oral edaravone in treatment cycles identical to intravenous edaravone for 48 weeks. At baseline, the average age was 59.9 years, 64.3% were male, 87% had concomitant use of riluzole, and the mean ALSFRS-R score was 40. The primary study outcome is treatment emergent adverse events. Exploratory endpoints included change from baseline in ALSFRS-R score and time to death, tracheostomy, or permanent assisted mechanical ventilation.

Clinical Benefits

AMX0035

Slowing of ALS-related Functional Decline

The primary outcome of the CENTAUR trial was assessed in the mITT population using a random-slope, shared-baseline, linear mixed model adjusted for age and pre-baseline ALSFRS-R slope. Secondary analytic approaches included a post-hoc change-from-baseline model in the mITT population and separately, a joint rank analysis with a mixed measures approach (MMRM) for missing data in the ITT population. Compared to the primary approach, the change from baseline model found a larger treatment difference of 2.92 in favor of the AMX0035 group (95% CI: 0.70 to 5.15, p=0.01). However, when using the ITT population and incorporating deaths when assessing function, the joint rank analysis was not statistically significant (p=0.079), with a difference in mean rank of 12 in the ITT population.

The manufacturer and FDA conducted several sensitivity analyses re-examining the primary outcome in the mITT population in the CENTAUR trial. These included testing for non-linearity by using a quadratic term and multiple imputation for missing data using data from the control arm (control-base imputation). When allowing for non-linearity of the ALSFRS-R score, the difference in ALSFRS-R still favored AMX0035, but was of smaller magnitude and not statistically significant (difference of 1.68 points, p=0.11) versus a difference of 2.32 (p-value=0.03) from the primary approach used in CENTAUR. When using the control-based imputation, there was also a smaller decline in ALSFRS-R score favoring AMX0035 that was statistically significant (difference of 1.87, p-value=.043).[49] However, the FDA's combined approach of using a quadratic term, the control-based imputation approach provided a lower estimate for the difference (1.68 point), and was not statistically significant.[49]

Survival

In CENTAUR, the composite outcome of death, tracheostomy or PAV occurred in 2.8% in the AMX0035 arm and 4.4% in the placebo arm (HR: 0.63, 95% CI: 0.11 to 3.9, p-value=0.59). Of note, PAV and tracheostomy occurred in a single patient in the placebo arm. When examining death alone, there was no difference in survival during the randomized phase of the CENTAUR trial (HR: 1.02, 95% CI: 0.15 to 9.75, p-value=0.98).[49]

The median time to death or death equivalent was 23.2 months in the group originally assigned to the treatment arm and 17.9 months in the group originally assigned to placebo (HR: 0.62, 95% CI: 0.4 to 0.95, p-value=0.03). At 12 months after randomization, survival in the groups originally randomized to AMX0035 and placebo were 80.9% (95% CI: 71.1 to 87.7) and 72.9% (95% CI: 58.0 to 83.3). At 24 months after randomization, survival for AMX0035 and placebo groups were 47.6% (95% CI: 36.8 to 57.6) and 37.0% (95% CI: 23.5 to 50.5), respectively.[49]

Secondary Outcomes

None of the prespecified endpoints in the CENTAUR trial were statistically significant. Regarding isometric muscle strength, the AMX0035 arm declined slightly less than the placebo group (difference of 2.8, 95% CI: -0.7 to 6.3, p=0.11). Non-prespecified analyses of the ATLIS sub scores suggested less decline in the upper-limb ATLIS score (difference of 4.3 in favor of AMX0035 group, 95% CI: 0.2 to 8.4, p=0.04), but not for the lower-limb ATLIS score (difference of 2.1 in favor of the AMX0035 group, 95% CI: -2.2 to 6.4, p=0.34). However, the FDA model, which did not assume linearity, estimated a smaller difference of 2.6 for the upper-limb ATLIS score in favor of AMX0035, but was not statistically significant (p=0.23). For respiratory capacity, the SVC declined modestly less for the AMX0035 group, but was not statistically significant (5.1% difference, 95% CI: -0.5 to 10.8, p=0.076). Lastly, the change in the exploratory biomarker of neuronal death (plasma pNF-H) was not statistically significant and was numerically lower in the placebo arm, which was the opposite from what was expected (difference of 37.7 pg/ml, 95% CI -24.3 to 89.8, p=0.26).[47,49,80]

During the randomized phase in the CENTAUR trial, hospitalization occurred in 17.4% in patients in the AMX0035 arm versus 27.7% in the placebo arm (HR: 0.59, 95% CI: 0.29 to 1.23, p-value=0.15).[49] In the OLE, the median time to first hospitalization is 31.8 months in the group originally randomized to AMX0035 and 14.1 months in the group originally randomized to placebo (HR: 0.61, 95% CI: 0.36 to 1.01, p-value=0.055).[48]

Oral Edaravone

Slowing of ALS-related Functional Decline

The manufacturer and FDA conducted a number of sensitivity analyses to test the robustness of the primary analysis (Table D5). Analyses using the ITT population, more appropriate approaches to

handle missing data, modeling non-linear decline in function, and assessing function and survival all corroborated the primary analysis.

Table D5. Post-hoc Sensitivity Analyses of Study 19 Primary Outcome (Change in ALSFRS-R Total Score from Baseline to Week 24)[54,90]

Analysis Method	Between-group differences in the adjusted mean LS mean ± SE (95% CI)	p-value
ANOVA with LOCF in mITT* (primary analysis)	2.49 ± 0.76 (0.99, 3.98)	0.0013
Post-hoc Sensitivity Analyses Performed by MTPA		
ANOVA with LOCF in ITT	2.37 ± 0.75 (0.89, 3.84)	0.0019
MMRM in mITT	2.81 ± 0.78 (1.27, 4.35)	0.0004
CAFS† in ITT	41.64 ± 12.30 (17.31, 65.96)	0.0009
Post-hoc Sensitivity Analyses Performed by FDA		
ITT	2.5 ± 0.8	0.0013
MMRM in mITT	2.83 ±0.76 (NR)	0.0003
CAFS† Wilcoxon Test	NR	0.0009
Non-linear cubic baseline model	2.32 ± 0.74 (NR)	0.0022

ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, ANOVA: analysis of variance, CAFS: the Combined Assessment of Function and Survival, CI: confidence interval, FDA: Food and Drug Administration, ITT: intention to treat, LOCF: last observation carried forward, LS Mean: least-squares means, mITT: modified intention to treat, MMRM: mixed model for repeated measures, MTPA: Mitsubishi Tanabe Pharma America, SE: standard error

*LOCF was applied to the patients who completed cycle 3 (reached 81 days after treatment initiation)

† Composite measure of ALSFRS-R change and death

Exploratory Analyses of ALSFRS-R in Study 19

Several post-hoc analyses of Study 19 demonstrated edaravone's benefit over placebo in the ALSFRS-R score. In a time-to-event analysis, edaravone treatment delayed a drop of one or more points on the ALSFRS-R items of walking and climbing stairs.[91] There was a treatment difference in favor of edaravone across all four ALSFRS-R domains (bulbar, fine motor, gross motor, and respiratory), with the largest treatment effect seen in the gross motor domain, which includes turning in bed, walking, and climbing stairs.[92] A greater proportion of trial participants had minimal deterioration in the ALSFRS-R score (1-to-2-point loss during the 24 weeks) in the edaravone arm versus placebo (39.1% vs. 13.2%).[92]

D3. Additional Uncertainties and Controversies

The major uncertainties and controversies for AMX0035 and oral edaravone are discussed in the main report. Additional methodological considerations for AMX0035 include the differential use of potentially disease-modifying drugs, potential for a single influential site that may have driven the

study findings, modest differential discontinuation rate in the treatment arm, and uncertainties about the biomarker finding.

At the time of randomization, far fewer patients in the AMX0035 arm were taking riluzole or intravenous edaravone (any: 71%; riluzole: 68%; edaravone: 25%; both: 22%) versus the placebo group (any, 88%; riluzole: 77%; edaravone: 50%; both: 40%). After randomization, more patients in the AMX0035 initiated riluzole and/or edaravone (16%) versus the placebo arm (4%).[49] The large difference in baseline use of potentially disease-modifying drugs may have biased towards no effect. However, the differential use post-baseline, may have biased towards an effect. Collectively, the magnitude and direction of the bias is uncertain.

In an analysis of potentially influential study sites on treatment efficacy, the primary analysis of ALSFRS-R score was no longer statistically significant after the removal of site 701 (n=13) with a lower mean difference of 1.90 points on the ALSFRS-R score at week 24 (slope difference=-0.079, SE=0.049; p=0.10). This site had an estimated within site treatment effect more than twice as large as the overall estimate (5.75 vs. 2.32 points). Furthermore, this same site had a substantive difference on time-to-death analyses during the OLE, with a within-site HR of 0.23, which is considerably smaller than the overall HR of 0.64. It is not clear if this finding is due to chance or something specific to this site.

Another area of potential concern was that fewer patients randomized to AMX0035 completed the study and remained on the study drug versus the placebo arm (67% vs. 77%). This was because more people in the AMX0035 arm terminated participation, discontinued because of an adverse reaction, and had disease progression.

Lastly, the proposed biomarker of neuronal death (pNF-H) was hypothesized to decrease with slowing of ALS progression because degeneration of motor neurons releases pNF-H into the cerebrospinal fluid (CSF), and then into the bloodstream.[93] Yet, in the CENTAUR trial, differences in pNF-H were not statistically significant, and numerically favored the placebo arm (lower in the placebo arm). It is unclear whether pNF-H is an appropriate biomarker to track treatment response, or if the plasma pNF-H is too insensitive compared to CSF measurements, since plasma values may be 10-fold lower than CSF even if highly correlated within individuals.[93,94] Clinical experts we spoke to did not lend much weight to these findings since pNF-H is harder to measure in the blood than from the CSF, and because it was not a validated biomarker for treatment response.

D4. Evidence Tables

Table D6. Study Quality[30-32,47,57]

Intervention	AMX0035	Edaravone			
Trial	**CENTAUR**	**Study 16**	**Study 18**	**Study 19**	**Witzel 2022**
USPSTF Rating					
Initial assembly of comparable groups at baseline	Yes	Yes	No	Yes	Yes
Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)	Uncertain*	Yes	Yes	Yes	Yes
Non-differential Follow-Up	Yes	Yes	Yes	Yes	NA
Patient/Investigator Blinding	Uncertain†	Yes	Yes	Yes	NA
Clear Definition of Intervention	Yes	Yes	Yes	Yes	Yes
Clear Definition of Outcomes	Yes	Yes	Yes	Yes	Yes
Selective Outcome Reporting	No	No	No	No	No
Valid Measurements	Yes	Yes	Yes	Yes	Yes
Intent-to-treat Analysis (RCT)	No - mITT	No - mITT	No - mITT	No - mITT	NA
Adjustment for all potential confounders (cohort studies)	NA	NA	NA	NA	Yesǂ
Approach to Missing Data	MAR	LOCF	LOCF	LOCF	Pairwise deletion
USPSTF Overall Rating	Fair	Good	Fair	Good	Good

LOCF: last observation carried forward, MAR: missing at random, mITT: modified intention to treat, NA: not applicable, RCT: randomized controlled trial, USPSTF: united states preventive services taskforce

*More patients in the AMX0035 group were initiated on riluzole and/or edaravone.

† Patient/Investigator blinding: A randomization error occurred resulting in first 17 patients receiving the drug, as a result the subsequent nine patients were assigned to placebo. During the exit questionnaire at the end of the randomized phase, a higher percentage of participants in the placebo arm were correctly able to guess what treatment they received. (Supplement Table D14)

ǂ Propensity score matching for site of disease onset, covariates of age at onset, disease duration, and baseline ALSFRS-R score

Table D7. Study Design – AMX0035

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
AMX0035					
CENTAUR Paganoni. NEJM. 2020.[47] NCT03127514	Double Blind, Placebo-Controlled Randomized Controlled Trial Trial Duration: 24 weeks	Adults with definite ALS and symptom onset within 18 months N = 137	**Arm I:** oral AMX0035 (3g sodium phenylbutyrate and 1g taurursodiol) once daily for three weeks then twice daily thereafter **Arm II:** Placebo (matching placebo comparator)	**Inclusion**: - Male or female (18 – 80) years old capable of giving informed consent - Diagnosed with Sporadic or Familial ALS - Less than or equal to 18 months since ALS symptom onset - SVC > 60% of predicted value for sex and height. - Stable dose of riluzole for 30-days or naive - Edaravone permitted as protocol modification after FDA approval **Exclusion:** - Presence of tracheostomy - Exposure to PB or TURSO within 3-months of study entry. - Pregnant or breastfeeding	**Primary Outcome [Week 24]:** Rate of decline in total score on ALSFRS-R from baseline through 24 weeks **Secondary Outcomes [Week 24]:** - Rate of decline in total isometric muscle strength (measured by ATLIS device) - Rate of decline in pNF-H - Rate of decline in SVC - Time to death, tracheostomy, permanent assisted ventilation, or hospitalization
CENTAUR OLE Paganoni. Muscle & Nerve. 2020.[48] NCT03488524	Open Label Extension of CENTAUR Trial Trial Duration: up to 132 weeks	Adults with definite ALS and symptom onset within 18 months N = 90	**Arm I:** AMX0035 (3g sodium phenylbutyrate and 1g taurursodiol twice daily thereafter).	- Same inclusion/exclusion criteria as above - Patients had to enter OLE within 28-days of the week 24 visit from the CENTAUR trial	**Primary Outcome [30 months]:** Survival and time to death (not pre-specified)

ALS: amyotrophic lateral sclerosis, ALSFRS-R: amyotrophic lateral sclerosis functional rating scale – revised, g: gram, N: total number, NCT: national clinical trial, OLE: open label extension, PB: sodium phenylbutyrate, pNF-H: plasma phosphorylated neurofilament heavy subunit, SVC: slow vital capacity

Table D8. Baseline Characteristics – AMX0035[47-49]

Trial		CENTAUR			CENTAUR OLE	
Length		24 weeks			30 months	
Arm		AMX0035	Placebo	Overall	AMX0035	Placebo
N		87	48	135	56	34
Age, years	mean (SD)	57.6 (10.45)	57.3 (7.56)	57.5 (9.5)	57.9 (10.57)	57.3 (7.56)
	median (min, max)	59.0 (NR)	57.5 (NR)	NR	NR	NR
Sex, n (%)	Male	61 (70.1%)	32 (66.7%)	93 (69%)	NR	NR
	Female	26 (29.9%)	16 (33.3%)	42 (31%)	NR	NR
Race, n (%)	White	82 (94.3%)	46 (95.8%)	128 (95%)	NR	NR
	Black	2 (2.3%)	1 (2.1%)	3 (2.2%)	NR	NR
	Asian	2 (2.3%)	1 (2.1%)	3 (2.2%)	NR	NR
	Other	1 (1.1%)	0 (0)	1 (0.7%)	NR	NR
BMI, mean (SD)		26.9 (4.42)	26.4 (5.81)	26.7 (4.9)	26.9 (4.39)	26.4 (5.81)
Months since ALS Symptom Onset, mean (SD)		13.5 (3.83)	13.6 (3.64)	13.5 (3.8)	13.5 (3.8)	13.6 (3.6)
Months since ALS Diagnosis, mean (SD)		5.9 (3.33)	6.3 (3.22)	6.0 (3.3)	5.9 (3.3)	6.3 (3.2)
Onset, n (%)	Bulbar	26 (30%)	10 (21%)	36 (27%)	26 (29%)	10 (21%)
	Limb	59 (67.8%)	38 (79.2%)	97 (71.8)	NR	NR
ALS Etiology, n (%)	Sporadic	NR	NR	NR	NR	NR
	Familial	9 (10.3%)	7 (14.6%)	16 (11.9%)	NR	NR
Diagnosis (El Escorial Revisited), n (%)	Definite	87 (100%)	48 (100%)	135 (100%)	NR	NR
	Probable	0 (0)	0 (0)	0 (0)	NR	NR
	Probable-Laboratory Supported	0 (0)	0 (0)	0 (0)	NR	NR
	Possible	0 (0)	0 (0)	0 (0)	NR	NR
Riluzole or edaravone use, n (%)	R or E	62 (71.3%)	42 (87.5%)	104 (77%)	64 (72%)	42 (88%)
	Riluzole	59 (67.8%)	37 (77.1%)	96 (71%)	61 (68%)	37 (77%)
	Edaravone	22 (25.3%)	24 (50.0%)	46 (34%)	23 (26%)	24 (50%)

Trial		CENTAUR			CENTAUR OLE	
	Both	19 (21.8%)	19 (39.6%)	38 (28%)	20 (22%)	19 (40%)
Time Since First Exposure to at Baseline, months, mean (SD)	**Edaravone**	3.5 (3.04)	3.6 (2.60)	NR	NR	NR
	Riluzole	5.7 (3.41)	5.5 (3.28)	NR	NR	NR
Slow Vital Capacity, % of predicted normal value		83.6 (18.17)	83.9 (15.92)	83.7 (17.4)	82.7 (18.99)	83.9 (15.92)
Pre-Baseline ALSFRS-R Slope, mean (SD)		0.95 (0.43)	0.93 (0.60)	0.94 (0.49)	0.96 (0.42)	0.93 (0.60)
ALSFRS-R Total Score, mean (SD)	**Overall**	35.7 (5.78)	36.7 (5.08)	36.0 (5.5)	35.6 (5.73)	36.7 (5.08)
	Bulbar	9.5 (2.4)	10.0 (2.6)	9.7 (2.5)	NR	NR
	Fine-Motor	8.0 (2.7)	8.0 (2.6)	8.0 (2.7)	NR	NR
	Gross-Motor	7.5 (2.8)	7.6 (2.6)	7.6 (2.8)	NR	NR
	Breathing	10.6 (1.9)	11.0 (1.8)	10.8 (1.9)	NR	NR
ATLIS Score - % of predicted normal value, mean (SD)	**Upper-Limb**	54.8 (24.4)	51.4 (25.2)	53.6 (24.6)	54.7 (24.16)	51.4 (25.22)
	Lower-Limb	57.6 (24.9)	57.1 (25.8)	57.4 (25.1)	56.9 (25.07)	57.1 (25.81)
	Total	56.8 (20.1)	53.9 (20.9)	55.8 (20.4)	56.4 (20.04)	53.9 (20.9)

ALS: amyotrophic lateral sclerosis, ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, ATLIS: accurate test of limb isometric strength, BMI: body mass index, E: edaravone, n: number, N: total number, NR: not reported, OLE: open label extension, R: riluzole, SD: standard deviation

Note: Baseline characteristics values for CENTAUR may have been updated based on data presented in FDA Briefing Document

Table D9. Key Efficacy for CENTAUR– AMX0035[47,49]

Trial			**CENTAUR**	
Population			**mITT**	
Arm			**AMX0035**	**Placebo**
N			87	48
ALSFRS-R Total Score	***Timepoint***		***Per Month***	
	LS Mean Change per Month (SE)		-1.24 (0.12)	-1.66 (0.16)
	Mean (SE) Change Per Month		-1.21 (0.12)	-1.74 (0.16)
	LS Mean Difference (SE) per Month, [95% CI], p-value		0.53 (0.21), [0.13, 0.93]	
	Timepoint		***Week 24***	
	Mean	LS Mean (SE)	29.06 (0.78)	26.73 (0.98)
		LS Difference (SE), [95%CI], p-value	2.32 (1.09), (0.18 to 4.47), 0.034	
	Mean Change from Baseline	LS Mean (SE) Change	-6.70 (0.68)	-9.62 (0.91)
		LS Mean Difference (SE), [95% CI], p-value	2.92 (1.13), [0.70, 5.15], 0.01	
ALSFRS-R Subdomain Scores	***Timepoint***		***Week 24***	
	Bulbar	Shared Baseline Estimate	9.70 (0.22)	
		LS Mean (SE)	8.20 (0.32)	7.68 (0.37)
		LS Difference (SE), [95% CI]	0.52 (0.33), [-0.13, 1.17]	
	Fine Motor	Shared Baseline Estimate	7.97 (0.24)	
		LS Mean (SE)	5.84 (0.30)	4.80 (0.38)
		LS Difference (SE), [95% CI]	1.04 (0.42), [0.20, 1.87]	
	Gross Motor	Shared Baseline Estimate	7.47 (0.24)	
		LS Mean (SE)	5.57 (0.34)	5.05 (0.41)
		LS Difference (SE), [95% CI]	0.51 (0.42), [-0.31, 1.34]	
	Breathing	Shared Baseline Estimate	10.77 (0.17)	
		LS Mean (SE)	9.49 (0.28)	9.13 (0.37)
		LS Difference (SE), [95% CI]	0.36 (0.45), [-0.53, 1.25]	
	Timepoint		***Week 24***	
	Est. % of Patients with Event, mean (SE)		19.3 (4.2)	33.1 (6.9)

Trial		CENTAUR	
Death, tracheostomy, or hospitalization	Hazard Ratio, mean (95%CI)	0.53 (0.27 to 1.05)	
Death or tracheostomy	***Timepoint***	***Week 24***	
	Est. % of Patients with Event, mean (SE)	2.8 (1.7)	4.4 (3.0)
	Hazard Ratio, mean (95%CI)	0.63 (0.11 to 3.92)	
Hospitalization	***Timepoint***	***Week 24***	
	Est. % of Patients with Event, mean (SE)	17.5 (4.1)	29.7 (6.6)
	Hazard Ratio, mean (95%CI)	0.54 (0.27 to 1.12)	

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale – revised, CI: confidence interval, Est.: estimate, SE: standard error

Note: Efficacy values for CENTAUR may have been updated based on data presented in FDA Briefing Document

Table D10. Key Efficacy for CENTAUR OLE– AMX0035[48,95]

Trial			CENTAUR OLE	
Arm			**Original AMX0035**	**Original Placebo**
Enrolled in OLE, N			56	34
Included in Survival Analysis, N			89	48
Timepoint			***Up to 30 months***	
Death	Mean HR, (95% CI), p-value		0.56 (0.34, 0.92), 0.023	
Death-Equivalent-Events	n (%)		6 (6.7%)	4 (8.3%)
Any Key Event-free Survival*	Mean HR, (95% CI), p-value		0.53, (0.35, 0.81), 0.003	
	Median duration, months (IQR)		14.8 (6.5, 29.1)	10.0 (4.0, 15.0)
First hospitalization-free Duration	Mean HR, (95% CI), p-value		0.56, (0.34, 0.95), 0.03	
	Median duration, months (IQR)		NR (6.9, NR)	14.1 (4.2, NR)
Tracheostomy or or PAV-free Survival†	Mean HR, (95% CI), p-value		0.51, (0.32, 0.84), 0.007	
	Median duration, months (IQR)		25.8 (14.8, 33.6)	18.5 (11.7, NR)
Survival	Median duration, months (95% CI)		25.0 (19.0, 33.6)	18.5 (13.5, 23.2)
	Probability of Survival at 12 months, % (95% CI)		80.9% (71.1%, 87.7%)	72.9% (58%, 83.3%)
	Probability of Survival at 24 months, % (95% CI)		51.6% (38.9%, 62.9%)	33.9% (19.4%, 49.1%)
	Riluzole use at baseline, HR (95% CI), p-value		0.54 (0.33, 0.89), 0.018	
	Edaravone use at baseline, HR (95% CI), p-value		0.53 (0.32 to 0.90), 0.019	
	Riluzole and edaravone use at baseline, HR (95% CI), p-value		0.53 (0.32 to 0.88), 0.016	
AMX0035 exposure	Median	months	8.8	1.9
		(range; first and third quartiles)	(0.1 - 33; 3.7 and 15.8)	(0 - 22.5; 0 and 9.1)
	Mean	months	10.6	4.7

CI: confidence interval, HR: hazard ratio, N: total number, NR: not reported, OLE: open label extension, PAV: permanent assisted ventilation

* Key events include all-cause death, tracheostomy, PAV, hospitalizations for ALS-related procedures or due to a severe or serious adverse event

† PAV: defined as permanent assisted ventilation >22 hours/day for >7 days

Table D11. Secondary Efficacy for CENTAUR – AMX0035[47]

Trial			CENTAUR	
Arm			AMX0035	Placebo
N			87	48
ATLIS Score - % of predicted normal value	***Timepoint***		***Per Month***	
	Total	LS Mean Change (SE)	-3.03 (0.19)	-3.54 (0.26)
	Upper-Limb	LS Mean Change (SE)	-3.04 (0.23)	-3.81 (0.31)
	Lower-Limb	LS Mean Change (SE)	-2.98 (0.24)	-3.36 (0.33)
	Timepoint		***Week 24***	
	Total	LS Mean (SE)	39.08 (1.99)	36.26 (2.22)
		Difference (95% CI), p-value	2.82 (-0.67 to 6.31), 0.1129	
	Upper-Limb	LS Mean (SE)	36.63 (2.32)	32.36 (2.59)
		Difference (95% CI), p-value	4.27 (0.16 to 8.38), 0.0420	
	Lower-Limb	LS Mean (SE)	41.17 (2.37)	39.09 (2.66)
		Difference (95% CI), p-value	2.09 (-2.23 to 6.41), 0.3424	
Plasma pNF-H level, pg/ml	***Timepoint***		***Per Month***	
	Least-Squares Mean Change (SE)		3.58 (3.19)	-2.34 (4.20)
	Timepoint		***Week 24***	
	Least-Squares Mean (SE)		406.95 (35.82)	374.25 (38.81)
	Least Squares Difference (95%CI), p-value		32.70 (-24.34 to 89.75), 0.26	
Slow Vital Capacity - % of predicted normal value	***Timepoint***		***Per Month***	
	Least-Squares Mean Change (SE)		-3.10 (0.31)	-4.03 (0.42)
	Timepoint		***Week 24***	
	Least-Squares Mean (SE)		66.17 (2.33)	61.06 (2.81)
	Least Squares Difference (95%CI); p-value		5.11 (-0.54 to 10.76); 0.0763	

ATLIS: accurate test of limb isometric strength, CI: confidence interval, LS: least squares, N: total number, pNF-H: phosphorylated neurofilament heavy subunit, SE: standard error

Table D12. Safety – AMX0035[47-49]

Trial		CENTAUR		CENTAUR OLE	
Arm		AMX0035	Placebo	Original AMX0035	Original Placebo
N		89	48	56	34
Treatment Discontinuation, n (%)		20 (23%)	10 (21%)	54 (96.4%)	34 (100%)
Duration of Exposure to Study Med, weeks, mean (SD)		19.7 (7.89)	21.5 (5.82)	NR	NR
Adverse Events, no. (%)	≥1 AE	86 (96.6%)	46 (95.8%)	NR	NR
	No. of distinct events	618	328	NR	NR
	Trial regimen interrupted due to AE	13 (15%)	6 (12%)	NR	NR
	Dose reduced due to AE	4 (4%)	0 (0%)	NR	NR
	Trial regimen discontinuation due to AE	18 (20.2%)	5 (10.4%)	NR	NR
	AEs related to intervention	13 (15%)	1 (2%)	NR	NR
Serious Adverse Events, no. (%)	≥1 SAE	11 (12.4%)	8 (16.7%)	NR	NR
	No. of distinct events	14	10	NR	NR
	Death	5 (5.6%)	2 (4.2%)	NR	NR
	≥1 SAE related to intervention	1 (1%)	1 (2%)	NR	NR
	Trial regiment discontinuation due to SAE	1 (1%)	3 (6%)	NR	NR
	SAE related to intervention	0 (0%)	0 (0%)	NR	NR
Adverse Events with ≥5% incidence in either group, no. (%)	Gastrointestinal disorders	60 (67%)	29 (60%)	NR	NR
	Musculoskeletal and connective-tissue disorders	38 (43%)	21 (44%)	NR	NR
	Injury, poisoning, and procedural complications	35 (39%)	23 (48%)	NR	NR
	Nervous-system disorders	33 (37%)	19 (40%)	NR	NR
	Infections and infestations	28 (31%)	21 (44%)	NR	NR
	Respiratory, thoracic, and mediastinal disorders	29 (33%)	10 (21%)	NR	NR
	General disorders and administration-site conditions	20 (22%)	13 (27%)	NR	NR
	Skin and subcutaneous-tissue disorders	16 (18%)	8 (17%)	NR	NR
	Psychiatric disorders	14 (16%)	9 (19%)	NR	NR
	Renal and urinary disorders	10 (11%)	8 (17%)	NR	NR
	Metabolism and nutrition disorders	10 (11%)	4 (8%)	NR	NR

Trial		CENTAUR		CENTAUR OLE	
	Cardiac disorders	7 (8%)	0 (0%)	NR	NR
	Eye disorders	5 (6%)	1 (2%)	NR	NR
Adverse Events, no, (%)	**Diarrhea**	19 (21.3%)	8 (16.7%)	NR	NR
	Constipation	13 (15%)	11 (23%)	NR	NR
	Nausea	16 (18.0%)	6 (12.5%)	NR	NR
	Muscular Weakness	18 (20.2%)	9 (18.8%)	NR	NR
	Back Pain	6 (7%)	4 (8%)	NR	NR
	Fall	25 (28.1%)	18 (37.5%)	NR	NR
	Contusion	8 (9%)	4 (8%)	NR	NR
	Headache	13 (14.6%)	11 (22.9%)	NR	NR
	Dizziness	9 (10.1%)	2 (4.2%)	NR	NR
	Viral Upper Respiratory Tract Infect.	10 (11.2%)	2 (4.2%)	NR	NR
	Urinary Tract Infection	7 (8%)	3 (6%)	NR	NR
	Dyspnea	9 (10.1%)	4 (8.3%)	NR	NR
	Respiratory Failure	5 (6%)	3 (6%)	NR	NR
	Fatigue	9 (10%)	3 (6%)	NR	NR
	Rash	5 (6%)	4 (8%)	NR	NR
	Insomnia	2 (2%)	3 (6%)	NR	NR
	Proteinuria	6 (7%)	2 (4%)	NR	NR
	Decreased Appetite	7 (8%)	2 (4%)	NR	NR
	Hypotension	2 (2%)	2 (4%)	NR	NR
	Atrial Fibrillation	2 (2%)	0 (0%)	NR	NR

AE: adverse event, N: total number, No.: number, NR: not reported, OLE: open label extension, SAE: serious adverse event

Note: Safety values for CENTAUR may have been updated based on data presented in FDA Briefing Document

Table D13. Sensitivity Analyses – AMX0035[47]

Trial			CENTAUR	
Arm			AMX0035	Placebo
N			87	48
ALSFRS-R Sensitivity Analyses	***Timepoint***		***Per Month***	
	Concomitant Riluzole	Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	-1.25 (0.12)	-1.68 (0.16)
		LS Difference (SE), [95% CI]	0.42 (0.20) [0.03, 0.81]	
	Concomitant Edaravone	Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	-1.27 (0.12)	-1.66 (0.16)
		LS Difference (SE), [95% CI]	0.39 (0.20) [-0.01, 0.79]	
	Concomitant Riluzole and Edaravone	Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	-1.27 (0.12)	-1.68 (0.16)
		LS Difference (SE), [95% CI]	0.41 (0.20) [0.01, 0.81]	
	Death or Death Equivalent	Shared Baseline Estimate	35.93 (0.50)	
		LS Mean (SE)	-1.26 (0.12)	-1.68 (0.16)
		LS Difference (SE), [95% CI]	0.42 (0.20) [0.03, 0.81]	
	Missing Data	Shared Baseline Estimate	35.79 (0.52)	
		LS Mean (SE)	-1.11 (0.11)	-1.44 (0.14)
		LS Difference (SE), [95% CI]	0.34 (0.17) [0.01, 0.67]	
	Timepoint		***Week 24***	
	Concomitant Riluzole	Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	28.99 (0.78)	26.66 (0.97)
		LS Difference (SE), [95% CI], p -value	2.34 (1.09) [0.19, 4.48]	
	Concomitant Edaravone	Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	28.92 (0.80)	26.77 (0.99)
		LS Difference (SE), [95% CI], p -value	2.15 (1.12) [-0.05, 4.35]	
		Shared Baseline Estimate	35.91 (0.50)	
		LS Mean (SE)	28.92 (0.80)	26.66 (0.99)

Trial			CENTAUR	
	Concomitant Riluzole and Edaravone	LS Difference (SE), [95% CI], p -value	2.26 (1.12) [0.07, 4.45]	
	Death or Death Equivalent	Shared Baseline Estimate	35.93 (0.50)	
		LS Mean (SE)	28.99 (0.78)	26.66 (0.97)
		LS Difference (SE), [95% CI], p -value	2.33 (1.08) [0.18, 4.47]	
	Missing Data	Shared Baseline Estimate	35.79 (0.52)	
		LS Mean (SE)	29.68 (0.65)	27.81 (0.82)
		LS Difference (SE), [95% CI], p -value	1.87 (0.93) [0.06, 3.69]	

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale – revised, CI: confidence interval, LS: least squares, SE: standard error

Table D14. CENTAUR Exit Questionnaire – Awareness of Treatment Assignment[47]

Questionnaire Response, n (%)	Investigator Response		Participant Response	
	AMX0035	Placebo	AMX0035	Placebo
N	89	48	89	48
Missing	11 (12.4)	8 (16.7)	9 (10.1)	7 (14.6)
Active	44 (49.4)	21 (43.8)	39 (43.8)	11 (22.9)
Placebo	34 (38.2)	19 (39.6)	41 (46.1)	30 (62.5)

Table D15. Study Design – Intravenous and Oral Edaravone

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
Intravenous Edaravone RCTs					
MCI186-16 Abe. ALS. 2014.[31] NCT00330681	Phase III double-blind, parallel-group, randomized controlled trial 12-week pre-observation period before the start of the first cycle 24-week treatment period In cycle 1, the drug was administered for 14 consecutive days followed by a 2-week drug-free period. In cycles 2-6, the drug was administered for 10 days followed by a 2-week drug-free period.	Adults with definite, probable, or probable-laboratory-supported ALS of grade 1 or 2 severity N= 205	**Arm I:** Edaravone IV (60 mg diluted with 100 mL saline) once a day via 60-minute infusion **Arm II:** Placebo (equivalent amount of saline)	**Inclusion:** - Adults aged 20-70 with a diagnosis of definite, probable, or probable-laboratory-supported ALS - Grade 1 or 2 (Japan ALS severity classification) - FVC of at least 70% - Duration of disease within three years - Change in ALSFRS-R score during 12-week pre-observation period before study drug administration of -1 to -4 points - Patients already on riluzole could continue as long as the regimen remained unchanged **Exclusion:** - Reduced respiratory function and complaints of dyspnea (ALSFRS-R score of 3 points or lower for any of the three items in dyspnea, orthopnea, and respiratory insufficiency in respiration) - Renal dysfunction with creatinine clearance of 50mL/min or below within 28 days before treatment	**Outcomes [Baseline to Cycle 6]:** - Change in ALSFRS-R - Change in FVC - Modified Norris Scale Score - ALS Assessment Questionnaire (ALSAQ-40) - Grip and pinch strength - Time to death or specified state of disease progression (incapable of independent ambulation, loss of function in upper limbs, tracheotomy, artificial respirator with intubation, or tube feeding

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
MCI186-17 Writing Group 17. ALS. 2017.[96] NCT00424463	Extension trial of Phase III DB RCT (MCI196-16) Primary analysis for extension period focused on E-E and E-P arms in cycles 7 - 12 All patients were offered open-label edaravone for the following 12 weeks (cycles 13 - 15)	Adults with definite, probable, or probable-laboratory-supported ALS of grade 1 or 2 severity N= 180	**Arm I:** E-E (edaravone in phase III, edaravone in extension **Arm II**: E-P (edaravone in phase III, placebo in extension) **Arm III**: P-E (placebo in phase III, edaravone in extension	**Inclusion:** - Patients who completed drug administration with discontinuation in preceding confirmatory study NCT00330681 **Exclusion:** - Patients with complications such as Parkinson's disease, schizophrenia, dementia, renal failure, or other severe complication - Anamnesis of hypersensitivity to edaravone - Participation in other clinical trials except NCT00330681	**Outcomes [Cycle 7-12]** - Change in ALSFRS-R - Number of patients with death or specified state of disease progression - Change in %FVC - AEs or adverse drug reactions
MCI186-18 [Grade 3] Abe. ALS. 2017.[32] NCT01492686	Phase III double-blind, parallel-group, randomized controlled trial 12-week pre-observation period before the start of the first cycle 24-week treatment period In cycle 1, the drug was administered for 14 consecutive days followed by a 2-week drug-free period. In cycles 2 and beyond, the drug was administered for 10	Adults with definite, probable, or probable-laboratory-supported ALS of grade 3 severity N= 25	**Arm I:** Edaravone IV (60 mg diluted with 100 mL saline) once a day via 60-min infusion **Arm II:** Placebo (equivalent amount of saline)	**Inclusion:** - Adults aged 20-70 with a diagnosis of definite, probable, or probable-laboratory-supported ALS - Grade 3 (Japan ALS severity classification) - FVC of at least 60% - Duration of disease within three years - Change in ALSFRS-R score during 12-week pre-observation period before study drug administration of -1 to -4 points - Patients already on riluzole	**Outcomes [Baseline to Cycle 6]:** - Change in ALSFRS-R - Change in FVC - Modified Norris Scale Score - ALSAQ-40 Score - Grip and pinch strength - Time to death or specified state of disease progression

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
	days followed by a 2-week drug-free period.			could continue as long as the regimen remained unchanged **Exclusion:** - Reduced respiratory function and complaints of dyspnea (ALSFRS-R score of 3 points or lower for any of the three items in dyspnea, orthopnea, and respiratory insufficiency in respiration) - Renal dysfunction with creatinine clearance of 50mL/min or below within 28 days before treatment	
MCI186-19 [Grade 1,2] Abe. Lancet Neurology. 2017.[30] NCT01492686	Phase III double-blind, parallel-group, randomized controlled trial 12-week observational period. Only patients with a decrease in ALSFRS-R score between 1-4 during this period were included in the randomized portion of the trial 24-week (6 cycles) treatment period. In cycle 1, the drug was administered for 14 consecutive days followed by a 2-week drug-free period. In	Adults with definite or probable ALS of grade 1 or 2 severity N= 137	**Arm I:** Edaravone IV (60 mg diluted with 100 mL saline) once a day via 60-min infusion **Arm II:** Placebo (equivalent amount of saline)	**Inclusion:** - Adults aged 20-75 with a diagnosis of ALS with independent living status (grade 1 or 2 in Japan ALS Severity Classification) - Decrease in ALSFRS-R score of 1-4 during 12-week observation period - Score of at least 2 on all 12 items of ALSFRS-R - FVC of at least 80% - Definite or probable ALS according to El Escorial and revised Airlie House criteria - Duration of disease from first symptom of 2 years or less - Patients already on riluzole	**Primary Outcome:** Change in ALSFRS-R score from baseline to end of cycle 6 (or at discontinuation if after the third cycle) **Secondary Outcomes:** - Change in FVC - Modified Norris Scale scores (limb, bulbar, total) -ALSAQ-40 score - ALS severity classification - Grip and pinch strength - Time to death or time

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
	cycles 2 and beyond, the drug was administered for 10 days followed by a 2-week drug-free period. All patients completing six cycles were offered open-label extension for an additional six cycles, up to cycle 12.			could continue as long as the regimen remains unchanged **Exclusion:** - Score of 3 or less on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency - History of spinal surgery after the onset of ALS - Creatine clearance 50 mL/min or less - Riluzole after the start of the observation period was prohibited	to a specified state of disease progression
MCI186-19 Extension Trial Writing Group. ALS. 2017.[63] NCT01492686	Open-Label Extension trial of Phase III DB RCT (MCI186-19) All patients who completed cycle 6 of the main phase III trial were offered open-label extension treatment for an additional six cycles (up to cycle 12)	Adults with definite or probable ALS of grade 1 or 2 severity N=123	Arm I: E-E (edaravone in phase III, edaravone in extension) Arm II: P-E (placebo in phase III, edaravone in extension)	**Inclusion:** - Adults aged 20-75 with definite or probable ALS with a duration of disease from the first ALS symptoms ≤ 2 years - Grade 1 or 2 in ALS Severity Score - Change in ALSFRS-R score during the 12-week pre-observation period before study drug administration of -1 to -4 points - Scores ≥ 2 points on all items of the ALSFRS-R (score of 4 required for each of the three items in dyspnea, orthopnea, and respiratory insufficiency in respiration - %FVC ≥ 80%	**Outcomes [up to cycle 12]** - Change in ALSFRS-R total score - Change in % FVC - Change in modified Norris scale score - Time to death or specified state of disease progression (disability of independent ambulation, loss of upper-limb function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech)

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
				Exclusion: - Reduced respiratory function and complaints of dyspnea - Renal dysfunction with creatinine clearance of 50 ml/min or below within 28 days of treatment	
SUNRISE Ishizaki. Neurology & Clin Neuroscience. 2021[59]	Post-Marketing Study	Japanese Adults with ALS N=805; 800 patients were included in the safety analysis set	Patients were prescribed edaravone based on routine clinical practice	Real-world study: patients diagnosed with ALS and prescribed edaravone for the first time during the surveillance period were included.	Patients were prescribed edaravone according to the prescribing information. The incidence of adverse drug reactions reported up to one year of follow-up was evaluated
Oral Edaravone					
Safety Study of Oral Edaravone Administered in Subjects with ALS Genge. 2021. ALS/MND Poster.[60] NCT04165824	Open-label Safety Trial of Oral Edaravone 48 weeks	Adults with ALS in North America, Western Europe, and Japan N = 185	Arm I: 105-mg dose of investigational oral edaravone administered in treatment cycles that replicate the dosing of IV edaravone This includes an initial treatment cycle with daily oral dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles consist of daily oral	**Inclusion:** - Adults aged 18-75 with definite, probable, probable laboratory-supported, or possible ALS, with a duration of disease ≤ 3 years - %FVC ≥ 70% - Functioning independently **Exclusion:** - Subjects undergoing treatment for malignancy or	**Primary Safety Outcomes [Week 24]** Adverse Events: - Total treatment-emergent adverse events (TEAES) - Serious TEAEs - TEAEs leading to death, discontinuation, or related to study drug

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
			dosing for 10 days of a 14-day period, followed by a 14-day drug-free period. Treatment cycles are every four weeks	those with a pending biopsy result - Subjects with a history of hypersensitivity to edaravone, any of the additives or inactive ingredients of edaravone, or sulfites	
Observational Studies					
Witzel. JAMA Neurology. 2022.[57]	Prospective, multicenter, propensity score–matched cohort study Study baseline was the start of the edaravone treatment for patients receiving edaravone or the first onsite visit for control patients. Follow-up included the time between baseline and death, discontinuation of edaravone treatment, last patient visit, or the end of data collection (March 31, 2020).	N=194 patients received ≥ 1 dose of edaravone (Safety cohort) N=260 patients in propensity score-matched sample for survival analysis (130 patients treated with edaravone/130 matched controlled with standard therapy) N=232 patients in propensity score-matched sample for disease progression	Arm I: IV edaravone + riluzole Arm II: Riluzole	**Inclusion:** For propensity score matching and effectiveness analyses, selected patients received at least four consecutive cycles of edaravone (16 weeks of treatment. Control patients have never been treated with edaravone. Both groups met El Escorial criteria for probable (including laboratory-supported) or definite ALS.	**Primary Outcome:** Change in ALSFRS-R score **Secondary Outcomes:** -Survival -Time to ventilation -Change in disease progression before vs. during treatment

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
		analysis (116 patients treated with edaravone/116 matched controlled with standard therapy)			

ALS: amyotrophic lateral sclerosis, ALSAQ-40: amyotrophic lateral sclerosis assessment questionnaire - 40, ALSFRS-R: ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, FVC: forced vital capacity, IV: intravenous, mg: milligram, mL: milliliter, N: total number, TEAE: treatment emergent adverse event

Table D16. Baseline Characteristics for RCTs – Intravenous Edaravone[30-32,55,74]

Trial		MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Length		24 weeks							
Arm		Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo
N		101	104	40	32	13	12	69	68
Age, years	mean (SD)	NR	NR	55.4 (9.6)	57.5 (10.4)	NR	NR	60.5 (10)	60.1 (10)
	median (min, max)	58.0 (29 - 73)	58.5 (28 - 75)	NR	NR	57 (47 - 70)	60 (44 - 71)	NR	NR
Sex, n (%)	Male	63 (62.4%)	69 (66.3%)	26 (65.0%)	20 (62.5%)	7 (53.8%)	6 (50%)	38 (55%)	41 (60%)
	Female	38 (37.6%)	35 (33.7%)	14 (35.0%)	12 (37.5%)	6 (46.2%)	6 (50%)	31 (45%)	27 (40%)
Race, n (%)	White	NA	NA	NA	NA	NA	NA	NA	NA
	Black	NA	NA	NA	NA	NA	NA	NA	NA
	Asian	101 (100%)	104 (100%)	40 (100%)	32 (100%)	13 (100%)	12 (100%)	69 (100%)	68 (100%)
	Other	NA	NA	NA	NA	NA	NA	NA	NA
BMI, median (min – max)		NR	NR	NR	NR	19 (16.2 - 24.5)	22.3 (16.1 - 24.7)	21.9 (3.6)*	21.8 (2.7)*
Months since ALS Symptom Onset, median (min - max)		15.6 (4.8 - 34.8)	14.4 (3.6 - 36)	NR	NR	16.8 (12.0 - 32.4)†	27 (9.6 - 33.6)†	13.56 (6)*†	12.72 (6)*†
Forced Vital Capacity, mean (SD)		95.53 (14.97)	95.78 (17.04)	NR	NR	83.9 (23.5)	86.48 (16.5)	100.5 (15.0)	97.4 (13.6)
Onset, n (%)	Bulbar	18 (17.8%)	20 (19.2%)	5 (12.5%)	7 (21.9%)	3 (23.1%)	0 (0%)	16 (23%)	14 (21%)
	Limb	83 (82.2%)	84 (80.8%)	35 (87.5%)	25 (78.1%)	10 (76.9%)	12 (100%)	53 (77%)	54 (79%)
ALS Etiology, n (%)	Sporadic	NR	NR	NR	NR	13 (100%)	11 (91.7%)	68 (99%)	66 (97%)
	Familial	NR	NR	NR	NR	0 (0%)	1 (8.3%)	1 (1%)	2 (3%)
ALS Severity (Japanese Classification), n (%)	Grade 1	36 (35.6%)	40 (38.5%)	NR	NR	0 (0%)	0 (0%)	22 (32%)	16 (24%)
	Grade 2	65 (64.4%)	64 (61.5%)	NR	NR	0 (0%)	0 (0%)	47 (68%)	52 (76%)
	Grade 3	NA	NA	NR	NR	13 (100%)	12 (100%)	0 (0%)	0 (0%)
Diagnosis	Definite	29 (28.7%)	21 (20.2%)	18 (45.0%)	9 (28.1%)	7 (53.8%)	2 (16.7%)	28 (41%)	27 (40%)
	Probable	52 (51.5%)	54 (51.9%)	22 (55.0%)	23 (71.9%)	4 (30.8%)	8 (66.7%)	41 (59%)	41 (60%)

Trial		MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Length		24 weeks							
Arm		Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo
(El Escorial Revisited), n (%)	Probable-Laboratory Supported	20 (19.8%)	28 (26.9%)	0 (0%)	0 (0%)	2 (15.4%)	2 (16.7%)	NA	NA
	Possible	0 (0%)	1 (1.0%)	0 (0%)	0 (0%)	NA	NA	NA	NA
Riluzole use, n (%)		90 (89.1%)	92 (88.5%)	37 (92.5%)	25 (78.1%)	10 (76.9)	11 (91.7)	63 (91%)	62 (91%)
ALSFRS-R Score Before Pre-Observation, median (min-max)		43.0 (31 - 48)	44.0 (35 - 48)	44.2 (2.4)*	44.2 (1.8)*	36.0 (25 - 42)	37.0 (29 - 43)	43.6 (2.2)*	43.5 (2.2)*
ALSFRS-R Score at Baseline, median (min-max)		41 (29 - 47)	42.0 (32 - 47)	42.5 (2.5)*	42.2 (2.2)*	32.0 (23 - 40)	35.0 (28 - 41)	41.9 (2.4)*	41.8 (2.2)*
Change in ALSFRS-R score during pre-observation, n (%)	-4, -3	29 (28.7%)	32 (30.8%)	8 (20.0%)	9 (28.1%)	4 (30.8%)	4 (33.3%)	12 (17%)	11 (16%)
	-2, -1	72 (71.3%)	72 (69.2%)	32 (80.0%)	23 (71.9%)	9 (69.2%)	8 (66.7%)	57 (83%)	57 (84%)

ALS: amyotrophic lateral sclerosis, ALSFRS-R: ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, BMI: body mass index, dpEESP2y: greater-efficacy-expected subpopulation with a diagnosis of 'definite' or 'probable' ALS and within two years of initial ALS symptom onset, n: number, N: total number, NR: not reported, SD: standard deviation

* mean (SD)

† converted from years to months

Table D17. Baseline Characteristics - Oral Edaravone[60]

Trial		MT-1186-A01
Length		24 weeks
Arm		Edaravone
N		185
Age, years	mean (SD)	59.9 (9.9)
Sex, n (%)	Male	119 (64.3%)
	Female	66 (35.7%)
Race, n (%)	White	NR
	Black	NR
	Asian	NR
	Other	NR
Months since ALS Symptom Onset, mean (SD)		1.56 (0.67)
Onset, n (%)	Bulbar	37 (20.0%)
	Limb	148 (80.0%)
Diagnosis (El Escorial Revisited), n (%)	Definite	45 (24.3%)
	Probable	77 (41.6%)
	Probable-Laboratory Supported	51 (27.6%)
	Possible	12 (6.5%)
Riluzole use, n (%)		161 (87.0%)
ALSFRS-R Total Score, mean (SD)		40.0 (4.5)

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, n: number, N: total number, SD: standard deviation

Table D18. Baseline Characteristics for Observational Study – Intravenous Edaravone[57]

Trial		Witzel 2022			
Length		*≥16 weeks of treatment (4 consecutive cycles)*			
Arm		Total: E	Total: Matched Cohort	EFAS: E	EFAS: Matched Cohort
N		130	130	52	52
Age, years, mean (SD)	mean (SD)	NR	NR	NR	NR
	median (min, max)	57.5 (NR)	56.7 (NR)	57.2 (NR)	57.8 (NR)
Sex, n (%)	Male	82 (63)	83 (64)	33 (63)	34 (65)
	Female	48 (37)	47 (36)	19 (37)	18 (35)
Race, n (%)	White	NR	NR	NR	NR
	Black	NR	NR	NR	NR
	Asian	NR	NR	NR	NR
	Other	NR	NR	NR	NR
Onset, n (%)	Bulbar	33 (25)	33 (25)	15 (29)	15 (29)
	Limb	97 (75)	97 (75)	37 (71)	37 (71)
Riluzole or edaravone use, n (%)	Riluzole	130 (100)	130 (100)	130 (100)	130 (100)
	Edaravone	130 (100)	0 (0)	130 (100)	0 (0)
	Both	130 (100)	0 (0)	130 (100)	0 (0)
ALSFRS-R Score at Baseline, median (min-max)		38 (NR)	39 (NR)	39.5 (NR)	39 (NR)

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, E: edaravone, EFAS: eligible within MCI186-19 study inclusion criteria, IQR: interquartile range, IV: intravenous, n: number, N: total number, NR: not reported, SD: standard deviation

Table D19. Key Efficacy for RCTs – Intravenous Edaravone[30-32,74]

Outcome		ALSFRS-R Total Score at Week 24							
Trial		MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Arm		Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo
N		101	104	40	32	13	12	69	68
Mean	LS Mean (SE)	38.08 (0.47)	37.43 (0.46)	NR	NR	30.32 (0.78)	30.39 (0.78)	NR	NR
	LS Difference (SE), [95%CI], p-value	0.65 (0.44), [-0.22, 1.52], 0.141		NR		-0.08 (1.08), [-2.32, 2.17], 0.945		NR	
Mean Change from Baseline	LS Mean (SE) Change	-5.7 (0.85)	-6.35 (0.84)	-4.58 (NR)	-7.59 (NR)	-6.52 (1.78)	-6.00 (1.83)	-5.01 (0.64)	-7.50 (0.66)
	LS Mean Difference (SE), [95% CI], p-value	0.65 (0.78), [-0.90, 2.19], 0.411		3.01 (1.33), [NR], 0.0270		-0.52 (2.46), [-5.62, 4.58], 0.835		2.49 (0.76), [0.99, 3.98], 0.0013	

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale – revised, CI: confidence interval, dpEESP2y: greater-efficacy-expected subpopulation with a diagnosis of 'definite' or 'probable' ALS and within two years of initial ALS symptom onset, LS: least squares, N: total number, NR: not reported, SE: standard error

Table D20. Key Efficacy - Oral Edaravone[60]

Trial		MT-1186-A01
Arm		Edaravone
N		185
ALSFRS-R Total Score	LS Mean Change from Baseline (95%CI)	-5.6 (-6.5, -4.8)
Forced Vital Capacity		-11.9% (-14.5, -9.3)

CI: confidence interval, ALSFRS-R: amyotrophic lateral sclerosis functional rating scale – revised, LS: least squares, N: total number

Table D21. Key Efficacy for Observational Study – Intravenous Edaravone[57]

Trial		Witzel 2022			
Arm		Total: E	Total: Matched Cohort	EFAS: E	EFAS: Matched Cohort
Timepoint		≥16 weeks of treatment (4 consecutive cycles)			
N		130	130	52	52
ALSFRS-R	Total Score, median (IQR)	*-0.88 (-1.56, -0.36)*	*-0.82 (-1.29, -0.35)*	*-1.02 (-1.52, -0.60)*	*-0.97 (-1.68, -0.50)*
	Change from baseline, median (IQR)	NR	NR	NR	NR
Survival Analysis	Probability of Survival at 12 months, %	83.60%	*90.60%*	*90.60%*	*88.20%*
	Probability of Survival at 24 months, %	*73.80%*	*59.70%*	*74.90%*	*70.10%*

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, E: edaravone, EFAS: eligible within MCI186-19 study inclusion criteria, IQR: interquartile range, IV: intravenous, N: total number, NR: not reported
Note: Italicized data is digitized

Table D22. Secondary Efficacy for RCTs – IV Edaravone[30-32,74]

Trial			MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Arm			EDV	PBO	EDV	PBO	EDV	PBO	EDV	PBO
N			101	104	40	32	13	12	69	68
Timepoint			***Week 24***							
Forced Vital Capacity	Mean	LS Mean (SE)	88.56 (1.59)	87.3 (1.56)	NR	NR	74.61 (2.5)	76.16 (2.48)	NR	NR
		Difference (SE), [95%CI], p-value	1.26 (1.46), [-1.63, 4.15], 0.390		NR	NR	-1.54 (3.42), [-8.68, 5.59], 0.657		NR	NR
	Mean Change from Baseline	LS Mean (SE) Change	-14.57 (2.41)	-17.49 (2.39)	-13.40 (NR)	-19.69 (NR)	-18.75 (4.58)	-15.69 (4.58)	-15.61 (2.41)	-20.4 (2.48)
		Difference (SE), [95% CI], p-value	2.92 (2.24), [-1.49, 7.33], 0.193		6.30 (3.10), [NR], 0.0467		-3.06 (6.28), [-16.12, 10.0], 0.631		4.78 (2.84), [-0.83, 10.40],0.0942	
Grip Strength (kg)	Mean	LS Mean (SE)	13.83 (0.43)	13.22 (0.42)	NR	NR	7.53 (0.78)	7.09 (0.80)	NR	NR
		LS Difference (SE), [95%CI], p-value	0.60 (0.40), [-0.18, 1.38], 0.130		NR	NR	0.44 (1.08), [-1.79, 2.68], 0.684		NR	NR

Trial			MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Arm			EDV	PBO	EDV	PBO	EDV	PBO	EDV	PBO
	Mean Change from Baseline	LS Mean (SE) Change	-4.81 (0.69)	-5.71 (0.69)	NR	NR	-3.06 (1.28)	-3.72 (1.31)	-4.08 (0.54)	-4.19 (0.56)
		Difference (SE), [95% CI], p-value	0.89 (0.64), [-0.37, 2.16], 0.165		NR	NR	0.66 (1.77), [-3.00, 4.33], 0.712		0.11 (0.64), [-1.15, 1.38], 0.8583	
Pinch Strength (kg)	Mean	LS Mean (SE)	2.83 (0.11)	2.62 (0.11)	NR	NR	1.32 (0.20)	1.47 (0.20)	NR	NR
		Difference (SE), [95%CI], p-value	0.21 (0.10), [0.01, 0.41], 0.038		NR	NR	-0.16 (0.28), [-0.74, 0.42], 0.576		NR	NR
	Mean Change from Baseline	LS Mean (SE) Change	-0.83 (0.15)	-1.03 (0.15)	NR	NR	-0.50 (0.24)	-0.27 (0.25)	-0.78 (0.14)	-0.88 (0.14)
		Difference (SE), [95% CI], p-value	0.20 (0.14), [-0.08, 0.48], 0.165		NR	NR	-0.23 (0.33), [-0.91, 0.45), 0.493		0.10 (0.16), [-0.23, 0.42], 0.5478	
Modified Norris Scale Scores	Total	LS Mean Change (SE)	-14.12 (2.05)	-16.15 (2.00)	-10.07 (NR)	-18.01 (NR)	-18.18 (3.80)	-17.76 (3.80)	-15.91 (1.97)	-20.80 (2.06)
		Difference (SE), [95% CI], p-value	2.03 (1.89), [-1.69, 5.75], 0.284		7.95 (3.63), [NR], 0.0326		-0.42 (5.22), [-11.27, 10.44], 0.937		4.89 (2.35), [0.24, 9.54], 0.0393	
	Limb Scale	LS Mean Change (SE)	NR	NR	NR	NR	NR	NR	-11.47 (1.61)	-14.91 (1.68)
		Difference (SE), [95% CI], p-value	NR	NR	NR	NR	NR	NR	3.44 (1.92), [-0.36, 7.24], 0.0757	
	Bulbar Scale	LS Mean Change (SE)	NR	NR	NR	NR	NR	NR	-4.44 (0.76)	-5.89 (0.79)
		Difference (SE), [95% CI], p-value	NR	NR	NR	NR	NR	NR	1.46 (0.90) [-0.33, 3.24], 0.1092	
ALSFRS-R Individual Subcomponents	Speech	Mean Change	NR	NR	NR	NR	NR	NR	-0.3	-0.4
		Delta	NR	NR	NR	NR	NR	NR	0.1	
	Salivation	Mean Change	NR	NR	NR	NR	NR	NR	-0.4	-0.5
		Delta	NR	NR	NR	NR	NR	NR	0.1	
	Swallowing	Mean Change	NR	NR	NR	NR	NR	NR	-0.3	-0.6
		Delta	NR	NR	NR	NR	NR	NR	0.3	
	Handwriting	Mean Change	NR	NR	NR	NR	NR	NR	-0.3	-0.3
		Delta	NR	NR	NR	NR	NR	NR	0.1	

Trial			MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Arm			EDV	PBO	EDV	PBO	EDV	PBO	EDV	PBO
	Eating Motion	Mean Change	NR	NR	NR	NR	NR	NR	-0.7	-1.0
		Delta	NR	NR	NR	NR	NR	NR	0.4	
	Dressing & Hygiene	Mean Change	NR	NR	NR	NR	NR	NR	-0.8	-1.0
		Delta	NR	NR	NR	NR	NR	NR	0.2	
	Turning in bed and adjusting bedclothes	Mean Change	NR	NR	NR	NR	NR	NR	-0.5	-0.8
		Delta	NR	NR	NR	NR	NR	NR	0.3	
	Walking	Mean Change	NR	NR	NR	NR	NR	NR	-0.4	-0.7
		Delta	NR	NR	NR	NR	NR	NR	0.3	
	Climbing Stairs	Mean Change	NR	NR	NR	NR	NR	NR	-0.6	-1.1
		Delta	NR	NR	NR	NR	NR	NR	0.5	
	Respiration (1) Dyspnea	Mean Change	NR	NR	NR	NR	NR	NR	-0.2	-0.4
		Delta	NR	NR	NR	NR	NR	NR	0.2	
	Respiration (2) Orthopnea	Mean Change	NR	NR	NR	NR	NR	NR	0.0	-0.1
		Delta	NR	NR	NR	NR	NR	NR	0.1	
	Respiration (3) Respiratory Insufficiency	Mean Change	NR	NR	NR	NR	NR	NR	0.0	0.0
		Delta	NR	NR	NR	NR	NR	NR	0.0	

ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, CI: confidence interval, dpEESP2y: greater-efficacy-expected subpopulation with a diagnosis of 'definite' or 'probable' ALS and within two years of initial ALS symptom onset, EDV: edaravone, IV: intravenous, Kg: kilogram, LS: least squares, N: total number, NR: not reported, PBO: placebo, SE: standard error

Table D23. Quality of Life – Intravenous Edaravone[30-32,74]

Outcome	ALSAQ-40 Score at Week 24							
Trial	MCI-16		MCI-16 dpEESP2y		MCI-18		MCI-19	
Arm	Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone	Placebo
LS Mean (SE) Change From Baseline	19.6 (3.82)	19.13 (3.79)	25.86 (NR)	28.99 (NR)	20.91 (5.71)	26.33 (5.34)	17.25 (3.39)	26.04 (3.53)
LS Mean Difference (SE), [95% CI], p-value	0.48 (3.5), [-6.44, 7.39], 0.892		-3.14 (6.76), [NR], 0.6442		-5.42 (7.49), [-21.05, 10.20], 0.477		-8.79 (4.03), [-16.76, -0.82], 0.0309	

ALSAQ-40: Amyotrophic Lateral Sclerosis Assessment Questionnaire – 40, CI: confidence interval, dpEESP2y: greater-efficacy-expected subpopulation with a diagnosis of 'definite' or 'probable' ALS and within two years of initial ALS symptom onset, LS: least squares, NR: not reported, SE: standard error

Table D24. Safety I – Intravenous Edaravone[30,31,63]

Trial		MCI186-16		MCI186-19	
Arm		Edaravone	Placebo	Edaravone	Placebo
N		102	104	69	68
Treatment Discontinuation, n (%)		NR	NR	2 (2.9%)	8 (11.8%)
AEs, no. (%)	≥1 AE	NR	NR	58 (84%)	57 (84%)
	Trial regimen discont. due to AE	NR	NR	1 (1.4%)	4 (5.9%)
	AEs related to intervention	NR	NR	2 (3%)	5 (7%)
Serious AEs, no. (%)	≥1 SAE	18 (17.6%)	24 (23.1%)	11 (16%)	16 (24%)
	Death	NR	NR	0 (0%)	0 (0%)
	SAE related to intervention	NR	NR	0 (0%)	0 (0%)
AEs with ≥5% incidence, no. (%)	Respiratory, thoracic, and mediastinal disorders	NR	NR	3 (4%)	2 (3%)
AE, no, (%)	Diarrhea	NR	NR	2 (3%)	4 (6%)
	Constipation	13 (12.7)	17 (16.3%)	8 (12%)	8 (12%)
	Nausea	NR	NR	NR	NR
	Muscular Weakness	7(6.9%)	9 (8.7%)	NR	NR
	Back Pain	NR	NR	4 (6%)	1 (2%)
	Fall	NR	NR	NR	NR

	Contusion	12 (11.8%)	5 (4.8%)	13 (19%)	9 (13%)
	Headache	8 (7.8%)	3 (2.9%)	4 (6%)	5 (7%)
	Dizziness	NR	NR	NR	NR
	Viral Upper Respiratory Tract Infection	NR	NR	5 (7%)	2 (3%)
	Respiratory Failure	NR	NR	NR	NR
	Fatigue	NR	NR	NR	NR
	Rash	7 (6.9%)	2 (1.9%)	5 (7%)	2 (3%)
	Insomnia	9 (8.8%)	10 (9.6%)	5 (7%)	4 (6%)
	Dysphagia	8 (7.8%)	12 (11.5%)	8 (12%)	10 (15%)
	Serious Dysphagia	NR	NR	8 (12%)	8 (12%)
	Glycosuria	6 (5.9%)	3 (2.9%)	NR	NR
	Gait disturbance	20 (19.6%)	16 (15.4%)	NR	NR
	Nasopharyngitis	22 (21.6%)	22 (21.2%)	3(4%)	5(7%)

AE: adverse event, E-E: edaravone in both RCT and extension, no.: number, NR: not reported, P-E: placebo in RCT and edaravone in extension, SAE: serious adverse event

Table D25. Safety II – Intravenous and Oral Edaravone[58-60]

Drug		IV Edaravone			Oral Edaravone
Trial		Safety Analysis Set (16 18, 19)		SUNRISE Post-Marketing	MT-1186-A01
Arm		Edaravone	Placebo	Edaravone	Edaravone
N		184	184	800	185
Treatment Discontinuation, n (%)		NR	NR	NR	24 (13%)
AEs, no. (%)	≥1 AE	161 (87.5%)	160 (87.0%)	97 (12.1%)	146 (78.9%)
	No. of distinct events	487	501	148	NR
	Trial regimen discont. due to AE	4 (2.2%)	10 (5.4%)	NR	11 (5.9%)
	AEs related to intervention	0 (0%)	0 (0%)	NR	36 (19.5%)
Serious AEs, no. (%)	≥1 SAE	32 (17.4%)	41 (22.3%)	30 (3.8%)	21 (11.4%)
	No. of distinct events	46	60	42	NR
	Death	4 (2.2%)	2 (1.1%)	NR	6 (3.2%)
	SAE related to intervention	0 (0%)	0 (0%)	NR	NR
AEs with ≥5% incidence, no. (%)	Gastrointestinal disorders	57 (31.0%)	68 (37.0%)	10 (1.3%)	NR
	Musculoskeletal and connective-tissue disorders	36 (19.6%)	39 (21.2%)	NR	NR
	Injury, poisoning, and procedural complications	39 (21.2%)	36 (19.6%)	4 (0.5%)	NR
	Nervous-system disorders	26 (14.1%)	23 (12.5%)	3 (0.4%)	NR
	Infections and infestations	63 (34.2%)	57 (31.0%)	4 (0.5%)	NR
	Respiratory, thoracic, and mediastinal disorders	26 (14.1%)	24 (13.0%)	1 (0.1%)	NR
	General disorders and administration-site conditions	41 (22.3%)	37 (20.1)	NR	NR
	Skin and subcutaneous-tissue disorders	47 (25.5%)	37 (20.1%)	8 (1%)	NR
	Psychiatric disorders	14 (7.6%)	20 (10.9%)	NR	NR
	Renal and urinary disorders	NR	NR	8 (1%)	NR
	Metabolism and nutrition disorders	NR	NR	7 (0.9%)	NR
AEs, no, (%)	Diarrhea	8 (4.3%)	9 (4.9%)	NR	NR

Drug		IV Edaravone			Oral Edaravone
	Constipation	23 (12.5%)	24 (13.0%)	NR	13 (7.0%)
	Nausea	4 (2.2%)	1 (0.5%)	NR	NR
	Muscular Weakness	8 (4.3%)	10 (5.4%)	NR	30 (16.2%)
	Back Pain	7 (3.8%)	7 (3.8%)	NR	13 (7.0%)
	Fall	NR	NR	NR	29 (15.7%)
	Contusion	27 (14.7%)	16 (8.7%)	NR	NR
	Headache	15 (8.2%)	10 (5.4%)	NR	11 (5.9%)
	Dizziness	3 (1.6%)	4 (2.2%)	NR	NR
	Viral Upper Respiratory Tract Infection	5 (2.7%)	3 (1.6%)	NR	1 (0.5%)
	Dyspnea	NR	NR	NR	10 (5.4%)
	Respiratory Failure	2 (1.1%)	5 (2.7%)	NR	3 (1.6%)
	Fatigue	NR	NR	NR	14 (7.6%)
	Rash	7 (3.8%)	4 (2.2%)	NR	NR
	Insomnia	14 (7.6%)	15 (8.2%)	NR	NR
	Hepatic function abnormality	2 (1.1%)	5 (2.7%)	35 (4.4%)	NR
	Atrial Fibrillation	NR	NR	NR	1 (0.5%)
	Dysphagia	18 (9.8%)	21 (11.4%)	NR	NR
	Serious Dysphagia	18 (9.8%)	19 (10.3%)	NR	NR
	Glycosuria	7 (3.8%)	3 (1.6%)	NR	NR
	Gait disturbance	23 (12.5%)	17 (9.2%)	NR	1 (0.5%)
	Nasopharyngitis	27 (14.7%)	29 (15.8%)	NR	NR

AE: adverse event, discont.: discontinuation, no.: number, NR: not reported

Table D26. Subgroup Analyses – Intravenous Edaravone[54,56]

		MCI-19			
		Between Group Difference in ALSFRS-R			
Subgroup		**Arm**	**N**	**LS mean (SE)**	**95%CI**
Age	**< 65**	PBO	44	2.31 (1.0)	(0.33, 4.30)
		E	46		
	≥ 65	PBO	22	2.73 (1.13)	(0.46, 5.01)
		E	22		
Duration of illness	**< 1 year**	PBO	32	2.56 (1.17)	(0.22, 4.90)
		E	27		
	≥ 1 year	PBO	34	2.22 (1.03)	(0.17, 4.28)
		E	41		
ALS Diagnosis	**Sporadic**	PBO	64	2.41 (0.76)	(0.90, 3.92)
		E	67		
	Familial	PBO	2	-	-
		E	1		
Initial Symptom	**Bulbar**	PBO	14	2.42 (1.46)	(-0.60, 5.43)
		E	15		
	Limb	PBO	52	2.44 (0.89)	(0.68, 4.21)
		E	53		
Diagnostic Criteria	**Definite ALS**	PBO	26	2.13 (1.19)	(-0.25, 4.51)
		E	28		
	Probable ALS	PBO	40	2.85 (0.99)	(0.88, 4.82)
		E	40		
ALSFRS-R at Baseline	**36 – 41**	PBO	56	1.6 (NR)	NR
		E			
	42 - 47	PBO	81	2.8 (NR)	NR
		E			

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised, ALS: amyotrophic lateral sclerosis, CI: confidence interval, E: edaravone, LS: least square, NR: not reported, PBO: placebo, SE: standard error

D5. Ongoing Studies

Table D27. Ongoing Studies

Title	Study Design	Treatment Arms	Patient Population	Key Outcomes	Status
AMX0035					
A Compassionate Use Protocol of AMX0035 for Treatments of Patients with Amyotrophic Lateral Sclerosis (ALS) NCT04516096	Open-Label Extension Estimated N= 30	1. AMX0035 orally twice daily	**Inclusion** - Patient who completed follow-up in AMX0035 trial - Established care with neurologist at the specialized ALS center involved in study **Exclusion** - Ongoing severe adverse events -Presence of unstable psychiatric disease, cognitive impairment, dementia, substance abuse that would impair ability to consent - Treatment, current or within 90 days from screening with any cell or gene therapies - Implantation of Diaphragm Pacing System	**Primary [Avg. 1 year]** - Treatment Emergent Adverse Events	Enrolling by invitation Primary & Study Completion: January 2023
Phase III Trial of AMX0035 for Amyotrophic Lateral Sclerosis Treatment (PHOENIX) NCT05021536	Phase III DB, PC, MC RCT Estimated N: 600	1. AMX0035 orally for 48 weeks: once daily for first three weeks then twice daily for remainder of study 2. Placebo	**Inclusion** - Adults with definite or clinically probable diagnosis of ALS - Time onset of first symptom of ALS should be <24 months prior to randomization - If participant is to be treated with riluzole and/or edaravone during trial, then treatment with it was started and maintained for at least 14 days for riluzole and a full treatment course for edaravone **Exclusion** - Presence of tracheostomy or permanent assisted ventilation SVC less than 55% - AST or ALT > 5 times upper limit of normal - Renal insufficiency	**Primary [Week 48]** - ALSFRS-R Slope Change and Survival - Adverse Events - Number of patients remaining in study until discontinuation **Secondary [Week 48]** - Rate of decline in SVC - QoL - Decline in King's and MiToS Stages - Ventilation Free Survival - Participant Health Status - Long-Term Survival [3 years]	Recruiting Primary Completion: Nov 2023 Study Completion: March 2024

Title	Study Design	Treatment Arms	Patient Population	Key Outcomes	Status
			- Class III/IV heart failure - Previous treatment for ALS with cell or gene therapies - Implantation of Diaphragm Pacing System		
Pharmacokinetics and Pharmacodynamics Study of AMX0035 in Patients With ALS NCT04987671	Open-label trial Estimated N= 14	*Period 1* 1. AMX0035 daily for 14 days *Period 2* 1. AMX0035 twice a day for up to 25 days	**Inclusion** - Adults with diagnosis of sporadic ALS (definite, probable, laboratory probable, possible) - If taking riluzole or edaravone, must be on stable dose for >30 days prior to day 1 **Exclusion** - Familial ALS - Forced vital capacity < 50% or presence of tracheostomy or under PV - AST or ALT > 3 times the upper limit of normal - Ongoing anemia - Class III/IV heart failure - Exposure to disallowed medications - See clinicaltrials.gov for extensive list	**Primary [Day 40]** - Blood concentration of PB and taurursodiol - Systemic exposure to PB and taurursodiol **Secondary [Day 40]** - Effect of demographic characteristics on blood concentration and systemic exposure of PB and taurursodiol - Effect of fixed dose combo of PB and taurursodiol on pharmacodynamic activity	Recruiting Primary Completion: June 2022 Study Completion: August 2022
Intravenous Edaravone					
Radicava (Edaravone) Findings in Biomarkers from ALS (REFINE-ALS) NCT04259255	Prospective, observational, longitudinal, multicenter study Estimated N: 300	**Arm I:** Edaravone for six treatment cycles up to 24 weeks	**Inclusion** - Adults with sporadic or familial ALS diagnosed as possible, probable, probable-laboratory supported or definite - Decision made to prescribe edaravone prior to screening - Naïve to edaravone or did not receive edaravone within one month **Exclusion** - Contraindication to edaravone - Participation in an interventional trial	**Primary [Cycles 1, 3, 6]** - Change in levels of 4-HNE, 8-F2, 3-NT, urate, MMP-9, neurofilaments, and 8-OHdG as potential biomarkers of oxidative stress, inflammation, or neurodegeneration **Secondary [Cycles 1,3,6]** - ALSFRS-R - Kings Clinical Staging - ALSAQ-40 - Appel ALS Score	**Recruiting** Study Completion: March 2023

Title	Study Design	Treatment Arms	Patient Population	Key Outcomes	Status
Oral Edaravone					
Safety Study of Oral Edaravone Administered in Subjects With ALS NCT04165824	Single Arm OL Safety Study Actual enrollment= 185	**Arm I:** Oral edaravone Initial treatment cycle with dosing for 14 days followed by 14-day drug-free period Subsequent cycles with 10 day dosing out of 14-day period followed by 14-day drug-free period	**Inclusion** - Adults aged 18 to 75 with definite, probable, probable-laboratory supported, or possible ALS according to El Escorial revised criteria - Living and functioning independently - Baseline FVC ≥ 70% - First symptom occurrence within 3 years of trial **Exclusion** - Presence or history of clinically significant disease - ALT or AST elevations greater than two times the ULN at screening - History of hypersensitivity to edaravone - Unable to take medications orally	**Primary [Week 48]** - Frequency and incidence of TEAEs **Secondary [Week 48]** - Change in ALSFRS-R from baseline - Time to death, tracheostomy, and permanent assisted mechanical ventilation	Completed but waiting on publication [interim results only]
Safety Extension Study of Oral Edaravone Administered in Subjects with Amyotrophic Lateral Sclerosis (ALS) NCT04577404	Phase III MC, OL Extension Study Estimated N= 140	**Arm I:** Oral edaravone administered once daily for 10 days out of 14, followed by 14-day drug-free period up to 96 weeks	**Inclusion** - Patients who successfully completed study MT-1186-A01 **Exclusion** - Not eligible to participate as judged by investigator - Unable to take medications orally or through a PEG/RIG tube	**Primary [Week 96]** - Safety and tolerability (AEs, adverse drug reactions, TEAEs) **Secondary [Week 96]** - Change from baseline in ALSFRS-R score - Time to death, tracheostomy, or permanent assisted mechanical ventilation	Recruiting Primary Completion: Sep 2023 Study Completion Date: Sep 2023
Efficacy and Safety Study of Oral Edaravone Administered in Subjects with ALS NCT04569084	Phase IIIb MC, DB RCT Estimated N= 380	**Arm I:** Oral edaravone once daily **Arm II:** Oral edaravone + placebo	**Inclusion** - Adults aged 18-75 with definite or probable ALS according to El Escorial - Baseline score ≥2 points on each individual item of ALSFRS-R at screening and baseline visits - Screening and baseline %FVC ≥70%	**Primary [Week 48]** - Change in ALSFRS-R from baseline **Secondary [Week 48]** - Change in % SVC - Change in ALSAQ-40	Recruiting Primary Completion: July 2023

Title	Study Design	Treatment Arms	Patient Population	Key Outcomes	Status
			- 1-to-4-point decline for eight weeks in ALSFRS-R score between screening and baseline visits - First symptom of ALS within two years **Exclusion** - History of spinal surgery after onset of ALS - Patients undergoing treatment for malignancy - Presence or history of any clinically significant disease - History of hypersensitivity to edaravone - Received stem cell therapy - Unable to take medications orally		Study Completion: July 2023
Efficacy and Safety Extension Study of Oral Edaravone Administered in Subjects With ALS **NCT05151471**	Phase IIIb MC, DB Extension RCT Estimated N=300	**Arm I:** Oral edaravone once daily up to 48 weeks **Arm II:** Oral edaravone administered for 10 days followed by 18-day placebo for up to 48 weeks	**Inclusion** - Successfully completed all study MT-1186-A02 visits and compliant with study drug **Exclusion** - Not eligible to continue in study as judged by the investigator - Unable to take medications orally or through PEG/RIG tube	**Primary** **[up to 96 weeks]** - Time from randomization to at least a 12-point decrease in ALSFRS-R or death **Secondary** **[up to 96 weeks]** - Combined Assessment of Function and Survival score - Change in ALSAQ-40 - Time from randomization to death, tracheostomy, or permanent assisted mechanical ventilation	Recruiting Primary Completion: June 2024 Study Completion: June 2024

AE: adverse event, ALS: amyotrophic lateral sclerosis, ALSAQ-40: amyotrophic lateral sclerosis assessment questionnaire - 40, ALSFRS-R: ALSFRS-R: amyotrophic lateral sclerosis functional rating scale - revised, DB: double-blind, MC: multicenter, N: total number, PB: sodium phenylbutyrate, PC: placebo-controlled, PV: permanent ventilation, QoL: quality of life, RCT: randomized controlled trial, SVC: slow vital capacity, TEAE: treatment emergent adverse event
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D6. Previous Systematic Reviews and Technology Assessments

We identified one published health technology assessment (HTA) conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and one previously conducted systematic literature review and meta-analysis evaluating the efficacy and safety of intravenous edaravone. Both are briefly summarized below.

CADTH

CADTH Canadian Drug Expert Committee Recommendation for Edaravone (Radicava – Mitsubishi Tanabe Pharma Corporation)

CADTH conducted a review in 2018 to assess reimbursement for intravenous edaravone. Four double-blind, placebo-controlled randomized controlled trials were included in the analysis of clinical benefit. Three of the four studies did not find statistically significant differences in the total ALSFRS-R score from baseline to the end of the treatment period. One study reported a statistically significant difference of -5.01 (SE: 0.69) in the ALSFRS-R score. Across the studies, no differences in survival (death or specified disease progression events), among treatment groups were observed. No major safety concerns were reported during the randomized trials, and this was reinforced in extension trials as well.

Based on a cost of $1,424 per 60mg of edaravone or $185,182 annually (as submitted by the manufacturer to CADTH), the incremental cost-utility ratio ranged from $1.4 million to $3.1 million per QALY gained in patients who have stage 1 or stage 3 ALS, respectively. CADTH reports that a 95% reduction in price is necessary to achieve a $200,000 per QALY threshold.

Based on the review, CADTH recommends reimbursement for intravenous edaravone for the treatment of ALS based on the following criteria: a patient is diagnosed with probable or definite ALS, has at least a 2-point score on each item of the ALSFRS-R, forced vital capacity ≥ 80%, symptoms for less than two years, and not requiring either non-invasive or invasive permanent ventilation. Additionally, a patient must be receiving care for ALS with a specialist.

Systematic Literature Review

Luo, L., et al. (2019). "Efficacy and safety of edaravone in treatment of amyotrophic lateral sclerosis – a systematic review and meta-analysis."[29]

Investigators conducted a meta-analysis to assess the efficacy and safety of intravenous edaravone in people with amyotrophic lateral sclerosis (ALS). A systematic literature review was conducted to identify studies that were double-blind, placebo-controlled randomized controlled trials enrolling patients between the ages of 20 and 75 with a diagnosis of definite, probable, probable laboratory-

supported, or possible ALS or a Japanese ALS severity classification of one to three. Inclusion criteria also included patients with a forced vital capacity of at least 60% and a change between -1 and -4 on the ALSFRS-R score identified three double-blind, placebo-controlled randomized controlled trials. Three randomized trials met the criteria and were included.

Across the three included trials, data from 367 patients were analyzed with 183 receiving intravenous edaravone and 184 receiving placebo. At week 24, the between-group difference in ALSFRS-R score was 1.63 (95% CI: 0.26 – 3.00, P=0.02). No significant difference was found in ALSAQ-40 score between the edaravone and placebo arms (MD: 4.74, 95% CI: -11.18 – 1.70, P-0.15) or any of the other secondary endpoints. An odds ratio of 1.22 (95% CI: 0.68 – 2.19, P=0.50) reflects no difference in the frequency of adverse events, and similar results were found with serious adverse events (OR: 0.71, 95% CI: 0.43 - 1.19, P=0.20). The investigators conclude these results further suggest intravenous edaravone has an encouraging efficacy and safety profile.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[97]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.{Jiang, 2021, 6024}
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

E2. Model Inputs and Assumptions

Model Inputs

Clinical Inputs

Model inputs were identified from the best available evidence and stakeholder engagement. The primary clinical inputs included the transition probabilities between alive health states, mortality, AMX0035 efficacy, oral edaravone efficacy.

Transition Probabilities

Figure 4.1 shows all possible transitions between health states in the model. Table E2 below provides 1-month transition probabilities between each of the alive health states. These estimates were modified from 3-month study estimates that assessed ALSFRS-R measures from the PRO-ACT database, a repository of repeated ALSFRS-R measures from 10,723 patients who participated in over 23 clinical trials (all of which were negative).[71,75] Patients on average were 56.2 years of age, majority male (60%), and most were on riluzole (77.5%). The treatment effects of AMX0035 and oral edaravone were applied to these monthly transition probabilities.

Table E2. 1-Month Transition Probabilities, King's Stages

	Stage 1	Stage 2	Stage 3	Stage 4a	Stage 4b	Dead
Stage 1	83.17	11.51	3.24	0.84	1.08	0.17
Stage 2	-	84.91	11.29	0.91	2.29	0.60
Stage 3	-	-	92.19	1.83	4.21	1.76
Stage 4a	-	-	-	94.41	4.21	1.39
Stage 4b	-	-	-	-	95.13	4.87

Mortality

A separate survival treatment effect of a HR = 1.00 for oral edaravone was applied based on the results of an open-label extension study (Table E3).[63] For AMX0035, a HR of 0.64 on mortality compared to SOC was seen in an open label extension study leading to a median difference in survival of 4.8 months.[48,49] The HR used in the model was calibrated upward since patients on AMX0035 also received a survival benefit from the delays in progression. Calibrating the HR to 0.74 led to the same median difference of 4.8 months in survival.

Table E3. Mortality Inputs

Parameter	Value	Source
AMX0035 ± SOC vs. SOC, HR	0.74*	Open label extension for CENTAUR & FDA Ad Comm Meeting[49]
Edaravone ± SOC vs. SOC, HR	1.00	Open label extension for Study 19[63]

CI: confidence interval, FDA: Food and Drug Administration, HR: hazard ratio, SOC: standard of care

*calibrated from 0.64 to match incremental median OS benefit.

AMX0035 Treatment Effectiveness

We assumed that, to the extent that it was effective, AMX0035 influenced the transitions between Stages 1 through 4a and 4b. We used the results from the CENTAUR trial that reported a mean rate of change in the ALSFRS-R score of -1.24 points per month with AMX0035 and -1.66 points per month with placebo.[47] This translated into a relative risk reduction of 25% for AMX0035.

Oral Edaravone Treatment Effectiveness

We assumed that, to the extent that it was effective, oral edaravone only influenced the transitions limited to Stages 1 through 3. The rationale was that no significant treatment effect was seen in Study 16 (broader early-stage ALS patients) and Study 18 (advanced ALS patients), which included patients with longer duration of disease, greater diagnostic uncertainty, and more reduced respiratory function.[30-32] Furthermore, the treatment effect on progression was limited to 35.1% of patients who entered the model based on the proportion of patients who met Study 19's narrower inclusion criteria from the broader Study 16 patient population, which was based on treatment benefit.[74] Time to progression results from Study 19 that resulted in a HR of 0.665 were used to modify the SOC transition matrix.[70,98] We assumed this treatment effect held for oral edaravone based on bioequivalence to IV edaravone.[73]

Adverse Events

The model considered serious adverse events that occur in ≥5% of either AMX0035, oral edaravone, or placebo treatment arms from the CENTAUR and MCI186-19 trials. There were no serious adverse events noted in the CENTAUR trial that occurred in ≥5% of patients. In the MCI186-19 trial, an equal proportion of dysphagia (12%) occurred in both groups. As the resultant incremental difference of treating this adverse event would be negligible, it was not included in the analysis.

Discontinuation

Evidence on discontinuation due to adverse events from CENTAUR and MCI186-19 were used to estimate discontinuation. We assumed individuals could discontinue treatment with AMX0035 and oral edaravone after the first cycle. Table E4 presents the 24-week treatment discontinuation rates due to adverse events reported from both pivotal trials. These were then converted to monthly probabilities and applied to each cycle in the model.

Table E4. AMX0035 and Oral Edaravone Treatment Discontinuation

Parameter	AMX0035	Oral Edaravone	Source
Treatment discontinuation due to adverse events	19.1%	1.4%	CENTAUR and Study 19[30,47]

Health State Utilities

Health state utilities were derived from publicly available data and applied to health states. We used consistent health state utility values across treatments evaluated in the model (Table E5). These utility estimates were from 217 patients who enrolled in the LiCALS multicenter, double-blind, randomized trial.[35] This trial assessed the use of lithium in patients with ALS.[99] EQ-5D questionnaires were used to estimate utility. The EQ-5D is a commonly used, generic, health-related quality-of-life questionnaire that estimates health status by measuring five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Within health state changes to utility and informal caregivers' utility will be considered pending data availability.

Table E5. Health State Utilities

Parameter	Value	Source
Stage 1	0.65 (95% CI: 0.59, 0.71)	Jones AR et al. 2014[35]
Stage 2	0.53 (95% CI: 0.49, 0.58)	Jones AR et al. 2014[35]
Stage 3	0.41 (95% CI: 0.36, 0.46)	Jones AR et al. 2014[35]
Stage 4a	0.27 (95% CI: 0.24, 0.30)	Jones AR et al. 2014[35]
Stage 4b	0.27 (95% CI: 0.24, 0.30)	Jones AR et al. 2014[35]

CI: confidence interval

Cost Inputs

All costs used in the model were updated to 2021 US dollars.

Drug Costs

For riluzole, we obtained an estimated per unit (oral tablet) acquisition cost from REDBOOK based on the lowest wholesale acquisition cost (WAC) of the generic versions. Cost for IV edaravone was based on the Centers for Medicare & Medicaid Services (CMS) average sales pricing (ASP) file. Drug costs are outlined in Table E6.

For oral edaravone, we obtained an estimated per unit mg acquisition cost from REDBOOK based on the WAC. For AMX0035, we assumed an annual parity price to IV edaravone resulting in approximately $240 per sachet (3g PB/1g TURSO) for AMX0035. The cost of both AMX0035 and oral edaravone will be updated as additional cost data become available.

Table E6. Drug Costs

Drug	WAC per Unit	Notes	Reference
Sodium phenylbutyrate / taurursodiol (AMX0035)	$238.69*	Per sachet (3g PB/1g TURSO)	Assuming annual price parity to IV edaravone
Oral Edaravone	$12.11	Per 1 mg	REDBOOK (accessed June 9, 2022)
IV Edaravone (Radicava®)	$20.991	Per 1 mg	CMS ASP file (accessed May 20, 2022)
Riluzole (generic)	$0.665	Based on lowest cost generic (50 mg Tab)	REDBOOK (accessed April 13, 2022)[100]

IV: intravenous, TBD: to be determined, WAC: wholesale acquisition cost

*Placeholder price

Non-Drug Costs

Non-drug costs were stratified by perspective below.

Health Care Sector Costs

Other non-drug costs included in the health care sector perspective were health care costs associated with the management of ALS (Table E7). The recurring costs were composed of costs for physician visits, outpatient facility, home health care, dietary supplements and cost of supplies for feeding tube and noninvasive ventilation, and medications other than ALS-specific drugs. Transitional costs were one-time fixed costs that occur at the transition of disease, such as the cost of a motorized wheelchair when loss of ambulation occurs.[72,101] Transitional costs included durable medical equipment, feeding tube, and hospitalization. These health state costs in Table 4.8 were estimated from another staging system (FT9) that is also based on the ALSFRS-R.[72] The authors adjusted the costs for King's from FT9 based on corresponding disease severity. For stage 4a and 4b, separate costs were not provided. As a result, the ratio of stage 4a:4b costs found from a prior economic analysis were applied to the singular stage 4 estimate.[70] In cases where patients progress in a non-sequential manner, the transitional costs were additive.

Table E7. Health Care Sector Costs by King's Stage in 2021 USD

	Stage 1	Stage 2	Stage 3	Stage 4a	Stage 4b
Recurring monthly costs	$668	$1,647	$2,314	$3,208	$4,052
Transitional costs	$266	$5,458	$12,276	$42,598	$53,084

Societal Costs

Recurring societal costs included patient absenteeism costs, informal care, transportation costs, and sundry informal costs (Table E8). Transitional societal costs included home and vehicle modification costs.[72] Societal recurring and transitive costs did not encompass health care sector costs. In cases where patients progressed in a non-sequential manner, the transitional costs were additive.

Table E8. Societal costs by King's stage in 2021 USD

	Stage 1	Stage 2	Stage 3	Stage 4a	Stage 4b	Death
Recurring monthly costs	$1,371	$3,721	$5,485	$8,094	$8,094	$0
Transitional costs	$266	$5,458	$15,041	$59,260	$59,260	$7,586

E3. Results

A more detailed breakdown of the costs for the conventional base-case results for oral edaravone and AMX0035 are shown in Tables E9 and E10.

Table E9. Detailed Drug and Health State Costs for Oral Edaravone

Treatment	Intervention Cost	SOC Cost	Recurring Monthly Health State Costs	Transitional Health State Costs	Total Costs
Oral Edaravone + SOC (Multidisciplinary Care ± Riluzole)	$427,000	$1,300	$100,000	$69,900	$598,000
SOC alone	-	$1,300	$100,000	$65,100	$166,000

Table E10. Detailed Drug and Health State Costs for AMX0035

Treatment	Intervention Cost	SOC Cost	Recurring Monthly Health State Costs	Transitional Health State Costs	Total Costs
AMX0035 + SOC (Multidisciplinary Care ± IV Edaravone ± Riluzole)	$260,000*	$120,000	$112,000	$77,800	$569,000
SOC alone	-	$105,000	$99,700	$65,400	$270,000

*Based on placeholder price

E4. Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in findings. Figures E1 and E2 present the results from a one-way sensitivity analysis from the health care sector perspective for both oral edaravone and AMX0035, respectively. Notably, the most influential inputs on the findings were the treatment effectiveness parameters on progression and mortality as well as treatment costs. Tables E11 and E12 present the lower and upper incremental cost-effectiveness ratios based on the lower and upper limit inputs for the most influential parameters. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating the proportion of simulations that were cost-effective at various commonly used willingness-to-pay thresholds. The results are shown in Tables E13 and E14.

Figure E1. Tornado Diagram for Oral Edaravone

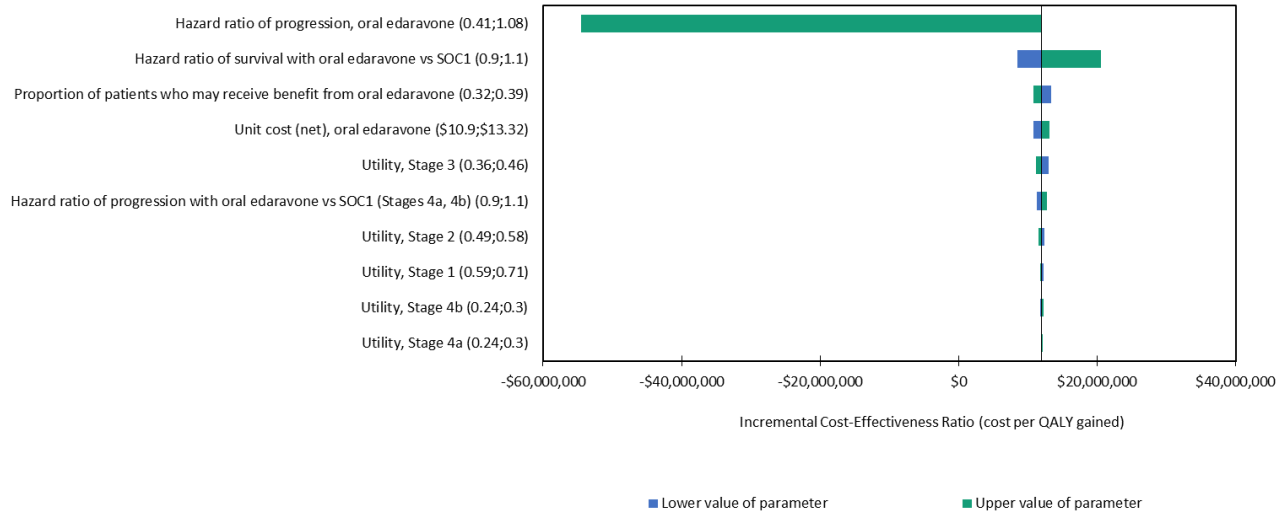


Table E11. Tornado Diagram Inputs and Results for Oral Edaravone versus Standard of Care with Multidisciplinary Care ± Riluzole

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Hazard ratio of progression, oral edaravone	$6,445,000	Dominated	0.41	1.08
Hazard ratio of survival with oral edaravone	$8,457,000	$20,594,000	0.90	1.10
Proportion of patients who may receive benefit from oral edaravone	$10,820,000	$13,410,000	0.32	0.39
Unit cost (net), oral edaravone	$10,802,000	$13,169,000	10.90	13.32
Utility, Stage 3	$11,143,000	$12,966,000	0.36	0.46
Hazard ratio of progression with oral edaravone vs. standard of care	$11,293,000	$12,737,000	0.90	1.10
Utility, Stage 2	$11,558,000	$12,351,000	0.49	0.58

CE: cost-effectiveness

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

Figure E2. Tornado Diagram for AMX0035

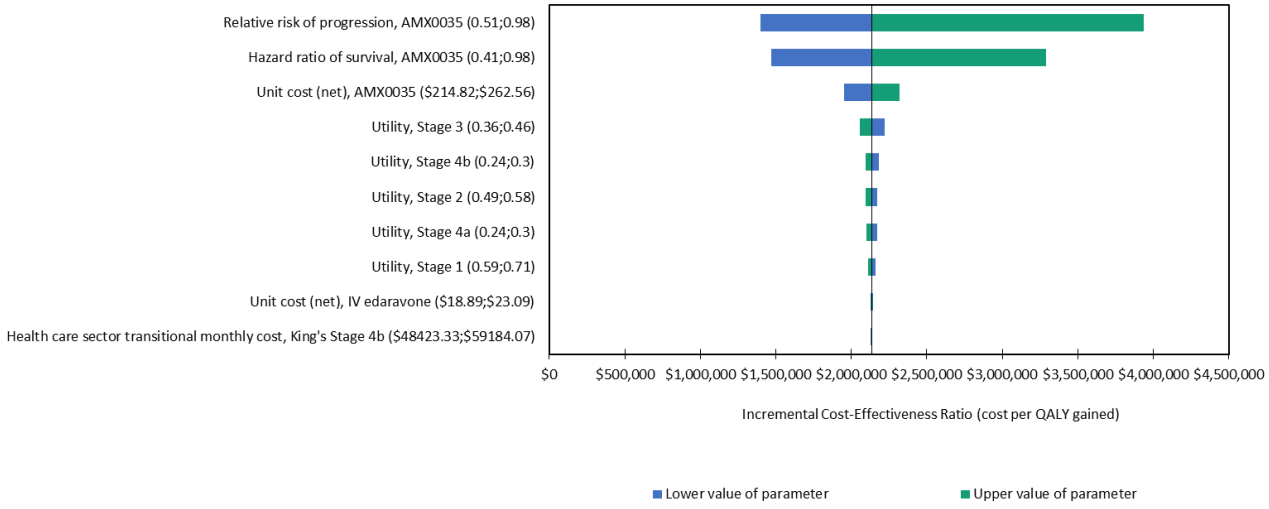


Table E12. Tornado Diagram Inputs and Results for AMX0035 versus Standard of Care with Multidisciplinary Care ± IV Edaravone ± Riluzole

	Lower Incremental CE Ratio**	Upper Incremental CE Ratio**	Lower Input*	Upper Input*
Relative risk of progression, AMX0035	$1,399,000	$3,937,000	0.51	0.98
Hazard ratio of survival, AMX0035	$1,470,000	$3,288,000	0.41	0.98
Unit cost (net), AMX0035	$1,950,000	$2,322,000	215	263
Utility, Stage 3	$2,056,000	$2,222,000	0.36	0.46
Utility, Stage 4b	$2,093,000	$2,182,000	0.24	0.30
Utility, Stage 2	$2,094,000	$2,171,000	0.49	0.58
Utility, Stage 4a	$2,100,000	$2,173,000	0.24	0.30

CE: cost-effectiveness

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

**Based on placeholder price

Table E13. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Oral Edaravone + SOC*	0.00%	0.00%	0.00%	0.00%
AMX0035 + SOC†	0.00%‡	0.00%‡	0.00%‡	0.00%‡

QALY: quality-adjusted life-year, SOC: standard of care

* Multidisciplinary Care ± Riluzole

† Multidisciplinary Care ± Riluzole ± IV Edaravone

‡ Based on placeholder price

Table E14. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Oral Edaravone + SOC*	0.00%	0.00%	0.00%	0.00%
AMX0035 + SOC†	0.00%‡	0.00%‡	0.00%‡	0.00%‡

evLY: equal value life-year, SOC: standard of care

* Multidisciplinary Care ± Riluzole

† Multidisciplinary Care ± Riluzole ± IV Edaravone

‡ Based on placeholder price

E5. Scenario Analyses

Table E15 presents the results from several scenario analyses that were described in the main report.

Table E15. Incremental Results from Scenario Analyses

Scenario 2: Treatment discontinuation with intervention and comparator once a patient reaches stage 4a or 4b	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$4,811,000	$3,289,000	$2,803,000
	AMX0035 + SOC†	SOC† alone	$1,665,000 ‡	$957,000‡	$814,000‡
Scenario 3: All patients start model at King's stage 1	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$6,812,000	$4,971,000	$4,236,000
	AMX0035 + SOC†	SOC† alone	$1,706,000‡	$955,000‡	$813,000‡
Scenario 4: Oral edaravone treatment continues through King's stage 4a and 4b	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$9,859,000	$5,524,000	$4,704,000
Scenario 5: All patients (100%) receive treatment benefit from oral edaravone	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$3,649,000	$2,505,000	$2,134,000
Scenario 6: No separate treatment effect on mortality for AMX0035 (i.e., HR=1)	**Health Care System Perspective**				
	Treatment	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	AMX0035 + SOC†	SOC† alone	$3,451,000‡	$2,051,000‡	$1,745,000‡
	Health Care System Perspective				

	Health Care System Perspective				
Scenario 2: Treatment discontinuation with intervention and comparator once a patient reaches stage 4a or 4b	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Oral Edaravone + SOC*	SOC* alone	$4,811,000	$3,289,000	$2,803,000
	AMX0035 + SOC†	SOC† alone	$1,665,000 ‡	$957,000‡	$814,000‡
Scenario 7: IV edaravone is not used as SOC regimen with AMX0035	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	AMX0035 + SOC†	SOC† alone	$2,040,000‡	$908,000‡	$773,000‡

* Multidisciplinary Care ± Riluzole ± Multidisciplinary Care
† Multidisciplinary Care ± Riluzole ± IV Edaravone ± Multidisciplinary Care
‡ Based on placeholder price
evLYG: equal value of life-year gained; IV: intravenous; LY: life-year; QALY: quality-adjusted life-year; SOC: standard of care

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report. We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

To our knowledge, there are no prior economic models that assess oral edaravone or AMX0035 as an addon to SOC compared to SOC alone for the treatment of ALS. Two economic models – one submitted to CADTH (IV edaravone) and one literature-based model by Thakore et al. 2020 (riluzole) are relevant for comparison to this current ICER review.

The manufacturer for IV edaravone submitted a cost-utility analysis to CADTH comparing IV edaravone + SOC versus SOC alone (which included interdisciplinary supportive care + riluzole). Given that our model assumes that the treatment efficacy for oral edaravone is in line with the IV form, the CADTH assessment of IV edaravone offers a useful comparison. The evaluation used a Markov model based the King's ALS staging system over a lifetime time-horizon using a three-month cycle length and a 1.5% discount rate for costs and health outcomes. The manufacturer assumed that the treatment effect would be constant across all ALS stages and that patients could only move to adjacent health states. These assumptions were revised in the CADTH reanalysis to allow for non-adjacent health state progression and treatment effects to vary according to stage.

Key differences between our model and the CADTH reanalysis of the manufacturer's submitted model include: baseline distribution of patient's according to King's staging (more patients at Stage 1 in the CADTH report vs. our model), continued treatment effect applied for edaravone from stages 1 through 4b, discount rate (1.5% in the CADTH report vs. 3% in our model), incremental CE ratio's calculated based on stratified results according to initial stage of disease (CADTH report vs. overall in our model), and utility estimates used (general population in the CADTH report vs. patient-derived in our model).

The base-case model from the manufacturer resulted in 0.97 QALYs for IV edaravone and 0.85 QALYs for SOC. The incremental cost-effectiveness ratio per QALY gained was approximately $1.56 million USD. Our model resulted in similar QALYs (0.93 for oral edaravone and 0.89 for SOC), with a higher incremental cost-effectiveness ratio per QALY gained ($11.99 million USD). The difference in incremental CE ratios is likely due to different costs used for King's stages, with the manufacturer's estimated health care costs being significantly higher than the ones we used. This led to much higher SOC costs resulting in a smaller incremental cost-effectiveness ratio compared to ours.

The base-case results from the CADTH reanalysis found an incremental benefit ranging between 0.156 life years (0.078 QALYs) for individuals initiating treatment in Stage 4A to 0.385 life years (0.267 QALYs) for individuals initiating treatment in Stage 1. Our model found an incremental benefit of 0.06 life years (0.04 QALYs), which is lower than the CADTH reanalysis. This finding is likely due to fewer patients starting at King's stage 1, the use of a higher discount rate, and the treatment effect only applied for King's stages 1-3 and only in 35% of patients in our model. The incremental cost utility ratio for IV edaravone from the CADTH reanalysis ranged between $1,441,000 Canadian dollars per QALY in stage 1 to $3,152,000 Canadian dollars per QALY in Stage 3 and it was not cost-effective at any stage of disease. Results from a limited societal-perspective analysis had only a marginal reduction in incremental cost-utility ratios. Price reductions of ≥95% would be required for the incremental cost utility ratio to reach a $200,000/QALY threshold.

Thakore et al. 2020 assessed the cost effectiveness of riluzole compared to best supportive care for the treatment of ALS. The evaluation used a Markov model based the FT9 staging system over a 5- and 10-year time-horizon using a one-month cycle length and a 3% discount rate for costs and health outcomes. Compared to our model, a fair comparison would be to identify the life years and QALYs accrued for riluzole in the scenario analysis performed using the King's staging system in Thakore 2020 and compare these outcomes to the SOC arm (which includes multidisciplinary care and riluzole) in the ICER model. Our model found that SOC accrued 2.64 life years and 0.89 QALYs over the lifetime time horizon. This result is lower than the 1.786 QALYs found in the scenario analysis in Thakore 2020 (life years accrued were not reported). This difference may be due to the differences in health state utilities used in the model and the disease progression staging system (FT9 vs. King's). Contributing to the contrasting results are the utility weights used in Thakore were

derived from patients at the author's institution and were higher across all King's stages compared to the ICER model.

Overall, the model structure used in our model was aligned with prior economic models in the literature and in an HTA assessment. Key differences included health state utility estimates, assumed relative treatment effects and baseline distribution of patients across King's staging.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we applied a prevalence estimate of 24,800,[2,9] incidence estimates (2 per 100,000 individuals),[8] and a death rate of 7,000 individuals per year to the 2022-2026 projected US population. Applying these sources resulted in an average estimated prevalence of 24,353 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 4,871 patients per year. Given we are assessing two new market entrants, we assumed that 50% of patients each year (N = 2,435) will initiate AMX0035 (added on to standard of care, i.e., riluzole ± edaravone ± multidisciplinary care) and the remaining 50% of patients each year (N = 2,435) will initiate oral edaravone (added on to standard of care, i.e., riluzole ± multidisciplinary care). We recognize that there may be other combinations of agents used in clinical practice, however, our analysis focused on those modeled in the cost-effectiveness analysis.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[102,103] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that oral edaravone will be added on to SOC and AMX0035 will be added on to SOC. In doing so, we assumed that no SOC treatments would be displaced by the entrance of these new treatments within the eligible population.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2021-2022, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.