Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Edaravone

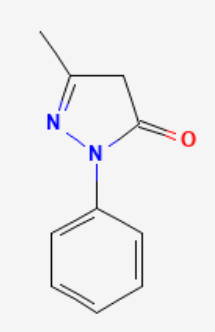
Evidence Summary

Edaravone has shown efficacy in treating ischemic stroke, intracerebral hemorrhage, and ALS. Efficacy in Alzheimer's disease will be assessed in an ongoing clinical trial.

Neuroprotective Benefit: Edaravone has neuroprotective benefits in patients with ALS and reduces postoperative cognitive impairment in people undergoing surgery. Efficacy in Alzheimer's patients will be assessed in an ongoing phase 2a trial.

Aging and related health concerns: Edaravone treatment improves outcomes for ischemic stroke, intracerebral hemorrhage, and coronary artery bypass surgery by reducing oxidative damage. It is not known if it can prevent age-related diseases.

Safety: Numerous meta-analyses in stroke, intracerebral hemorrhage, and ALS have shown that incidences of adverse events with edaravone are not significantly different from placebo. However, thrombotic events are associated with chronic intravenous access.

Availability: Rx for the treatment of ALS	**Dose**: In ALS patients, edaravone is administered intravenously, typically at 30 mg twice daily for 1-6 weeks (usually with on-off cycles). Oral formulations are being tested in clinical trials.	**Chemical formula:** $C_{10}H_{10}N_2O$ **MW**: 174.20  Source: PubChem
Half life: 4.5-6 hours	**BBB**: penetrant	
Clinical trials: Phase III trials of edaravone included up to 140 patients with ALS.	**Observational studies**: Postmarketing studies in the US reported over 3,000 patients with ALS who have been prescribed with edaravone.	

What is it? Edaravone is a synthetic free radical scavenger marketed for treating acute ischemic stroke in Japan and China. In 2015, it was also approved for amyotrophic lateral sclerosis (ALS) treatment in Japan. It has been marketed as Radicut® (MCI-186) in Japan by Mitsubishi Tanabe Pharma since 2001 and as Arone® in India by Edinburgh Pharmaceuticals. In February 2016, Mitsubishi Tanabe Pharma America Inc. was established to accelerate approval of edaravone for treating ALS in the US. On May 5, 2017, MT Pharma America announced FDA approval of edaravone (Radicava®) to treat ALS. It was the first new drug to treat ALS in 22 years. It is sold under the brand name Radicava®.

Edaravone exerts neuroprotective benefits by scavenging free hydroxyl radicals and peroxynitrite radicals that are associated with neuronal death and preventing lipid peroxidation from these free radicals (drugbank.com).

Currently approved forms of edaravone require intravenous infusions. Oral formulations of edaravone are under clinical development. In October 2019, Mitsubishi Tanabe Pharma's MT-1186, an oral suspension of edaravone, received Fast Track designation from the FDA. Treeway B.V., a clinical-stage biotechnology company, is also developing an oral edaravone formulation, TW001, for ALS and Alzheimer's disease (Treeway.nl).

Neuroprotective Benefit: Edaravone has neuroprotective benefits in patients with ALS and reduces postoperative cognitive impairment in people undergoing surgery. Efficacy in Alzheimer's patients will be assessed in an ongoing phase 2a trial.

Types of evidence:

- 1 meta-analysis and systematic review in ALS patients
- 3 clinical trials examining postoperative cognitive impairment in patients undergoing surgery
- 2 open-label clinical studies in ALS patients
- 1 retrospective analysis in ALS patients
- 2 post-marketing studies in ALS patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested whether edaravone treatment prevents dementia or age-related cognitive decline. In a clinical trial of patients undergoing carotid endarterectomy (surgery to remove plaque buildup to reduce the risk of stroke), the incidence of postoperative cognitive impairment was lower in people receiving edaravone pretreatment (2%; 1 out of 55 patients) than controls (12%; 11 out of 92 patients) (Ogasawara et al., 2005).

In a double-blind randomized controlled trial (RCT) in 80 elderly patients undergoing hip joint replacement surgery, edaravone treatment (0.5 mg/kg, i.v.) 10 minutes prior to beginning of surgery resulted in higher cognitive scores (MMSE) on day 3 than those who received the saline control (25.98 ± 1.99 vs 24.86 ± 1.86; $p = 0.003$)(Zhang et al., 2020). By day 7, cognitive scores were restored to baseline levels in both groups. Significant increases in plasma markers of inflammation, IL-6, S100β (brain injury marker), and MMP-9, were observed at the end of surgery and on postoperative day 3 in both groups, but edaravone pretreatment reduced these levels. Patients receiving edaravone pretreatment had significantly higher levels of the antioxidant SOD and significantly lower levels of the lipid peroxidation marker, MDA, compared to the saline control group.

In another double-blind RCT in 152 elderly patients undergoing hip replacement surgery, a single infusion of edaravone (30 mg, i.v.) 30 minutes before surgery significantly reduced cognitive deficits and the incidence of postoperative delirium 7 days after surgery (12 cases, 15.0% in the edaravone group vs 25 cases, 31.3% in the control group; $p<0.001$)(Xie et al., 2021). The edaravone-treated group had significantly higher scores on the modified telephone interview for cognitive status and activities of daily

life at 1-month and 12-month post-surgery compared to the saline control group. The length of hospital stay was shorter in the edaravone-treated group than the saline control group; at 1-month post-surgery, 10 patients (12.5%) in the edaravone group and 18 patients (22.5%) in the control group developed perioperative neurocognitive disorders ($p<0.05$). At 12 months after surgery, 4 patients (5.0%) and 8 patients (10.0%) in the edaravone and saline control groups, respectively, experienced neurocognitive disorders. The edaravone-treated group also had significantly lower concentrations of serum inflammation biomarkers, CXCL13 and IL-6. However, for both CXCL13 and IL-6, the saline control group had higher baseline levels (before anesthesia), so it is not clear if the differences in these biomarkers are due to edaravone treatment or attributed to group differences prior to the treatment.

Human research to suggest benefits to patients with dementia:
None available. A biotech company, Treeway B.V., has developed an oral formulation of edaravone (TW001) and ADDF is funding a phase 2a clinical trial to test this formulation in Alzheimer's patients (ADDF news room).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
The vast majority of studies testing the effects of edaravone are in models of significant brain pathology or insult. While some controversies remain for efficacies of antioxidants in general, edaravone has several additional advantages, such as its ability to readily cross the blood-brain-barrier, reduce inflammation, and inhibit apoptosis (Jiao et al., 2015). Edaravone has been tested most extensively in clinical trials for ALS.

ALS clinical trials: In a 2019 systematic review and meta-analysis of 3 double-blind RCTs including a total of 367 patients with ALS, edaravone treatment (60 mg/day, i.v.) for 24 weeks resulted in a significant difference in the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score, the primary outcome, compared to patients receiving placebo (Luo et al., 2019). All 3 trials were from Japan and performed by the same teams. None of the secondary endpoints showed statistically significant differences between edaravone and placebo groups (ALSAQ-40 score, forced vital capacity %, Modified Norris Scale, grip strength, and pinch strength).

In a retrospective analysis of 57 consecutive ALS patients, of whom 27 were treated with edaravone and 30 were not, edaravone treatment (14 days followed by 2-week drug-free, subsequently 5 days/week for 2 weeks drug, followed by 2-week drug-free) for a mean treatment duration of 8.8 months resulted in slower progression and better prognosis compared to those who did not receive edaravone (Okada et al., 2018). ALSFRS-R scores at baseline were more severe in the edaravone group (30.0 ± 12.1) than in

the control group (38.7 ± 6.3), and changes in ALSFRS-R scores from baseline to 6 months was significantly reduced in the edaravone group, compared to the control group. However, at 12 and 18 months, changes in ALSFRS-R scores were not significantly different between the groups.

ALS patients with low serum creatine have faster disease progression and shorter survival (Guo et al., 2021). At baseline, serum creatine levels were lower in the edaravone group (0.44 ± 0.15 mg/dl) than those in the control group (0.57 ± 0.15 mg/dl). Serum creatine levels at 6 and 12 months were significantly improved in the edaravone group compared to the control group where they decreased significantly (Okada et al., 2018).

In a Kaplan-Meier curve, edaravone treatment showed significant improvement in survival compared to ALS patients not on edaravone (Okada et al., 2018). Median tracheostomy-free survival lengths were 61.0 and 32.5 months in the edaravone and control groups, respectively (HR=0.37, 95% CI 0.20-0.74).

While these findings are compelling, the study has several caveats (Okada et al., 2018). The control group did not receive a placebo and included a higher number of patients with bulbar-onset-type, which is often a more aggressive form of ALS. It is also possible that the edaravone group received greater medical care due to the multidisciplinary approach to the treatment.

In an open-label clinical study in 123 ALS patients (ALS MCI186-19, or Study 19), where edaravone treatment (60 mg, i.v.) for 24 weeks was followed by a 24-week open-label extension, the projected ALSFRS-R decline for placebo was greater than for edaravone ($p<0.0001$)(Shefner et al., 2020). In patients who switched from placebo to edaravone, ALSFRS-R slope approached that of patients receiving edaravone for 48 weeks. These findings from post-hoc analyses suggest that edaravone is beneficial in ALS patients even after receiving the placebo initially for 6 months, and efficacy is maintained for up to 1 year.

In contrast, in an open-label clinical study in 31 ALS patients in North-Eastern Italy, edaravone treatment (Avone®, a commercially available edaravone bioequivalent of Radicut®) for 2 weeks each month for 6 months did not result in any differences in functional measures compared to baseline (Fortuna et al., 2019). In edaravone-treated patients, creatinine values were significantly decreased at 3 and 6 months ($p=0.0078$ and 0.030, respectively), which is associated with poorer prognosis, and quality of life also worsened (measured by ALSAQ5 score) at 3 and 6 months ($p=0.0005$ and 0.0078, respectively). In a larger Italian observational study of 331 ALS patients treated with edaravone and 290 matched historical controls, edaravone treatment did not significantly change disease progression or respiratory function

(Lunetta et al., 2020). The different outcomes observed in the Italian population may, in part, be due to differences in the genetics of ALS in Japanese vs. European people. For example, SOD1 mutations are more common in Japanese people C9Orf72 expansions are more common in European people (Zou et al., 2017). These different mutations may affect oxidative stress pathways differently, making responses to edaravone dissimilar.

In a review of ALS clinical trials and postmarketing data across different countries, the findings were mixed and not consistent (Ortiz et al., 2020). Generally, clinical trials have shown efficacy in early ALS patients with selective criteria, but outcomes were different depending on the country where the clinical trials took place. Findings of benefits with edaravone in early ALS disease are based on the phase 3 clinical trial that overall failed to show statistically significant differences between edaravone treatment and placebo, but in a post-hoc study with stringent early-stage ALS criteria, the primary outcome showed a significant reduction in the ALSFRS-R score over the placebo group. A subsequent post-hoc analysis (the MCI-186 Study 19) showed that edaravone favored each of the ALSFR-R score domains and similar benefits were seen in motor and bulbar onset ALS patients. However, in a parallel study of the MCI-186 study with a different group of patients with less selective criteria (including early and late stages of ALS), there were no statistically significant differences in the ALSFR-R score over placebo (Writing Group et al., 2017). An open-label extension of study MCI-186-19, where 24 weeks of treatment was followed by an open-label extension of 24 weeks, reported that patients receiving edaravone for 48 weeks showed less functional decline (measured by ALSFR-S scores) over patients who received 24 weeks of placebo, followed by 24 weeks of edaravone (Takei et al., 2017).

Postmarketing analysis in the US included 3007 patients who were prescribed with edaravone (of whom 67% of patients were using edaravone combined with riluzole) and drug ineffectiveness was reported in more than 50 cases (Jackson et al., 2019; Ortiz et al., 2020). There is limited information on the efficacy of edaravone in the US due to the limited number of reports on efficacy.

In an early postmarketing study carried out at the Tel Aviv Sourasky Medical Center in Israel, 22 patients who opted for edaravone treatment and 71 untreated ALS patients were compared (Abraham et al., 2019). Muscle strength, ALS Functional rating scale (ALSFRS-R), and respiratory function were similar between edaravone treated and untreated patients; edaravone-treated and untreated patients showed no significant differences in the rate of monthly decline of ALSFRS-R, manual muscle testing (MMT) score and forced vital capacity (FVC). In fact, edaravone-treated patients showed a higher death rate, but this difference failed to reach statistical significance.

Preclinical data from models of Alzheimer's and cognitive decline: In an *in vitro* experiment, edaravone bound to the 13-18 amino acid sequence of Aβ42, inhibited Aβ aggregation, and disaggregated already-formed Aβ fibrils (Jiao et al., 2015). In human neuroblastoma cells, edaravone dose-dependently protected neurons from cell death. *In vivo* experiments in a mouse model of Alzheimer's disease (APPswe/PS1) showed that edaravone prevented cognitive deficits and reduced Aβ levels, cerebral amyloid angiopathy, neuronal and dendritic loss, inflammation, and tau-phosphorylation. Notably, a 3 month-treatment of edaravone (from 9-12 months old) was effective in protecting against cognitive deficits even after the onset of Aβ deposition. Other than its free radical scavenging properties, edaravone suppressed BACE1 (involved in amyloidogenesis) and GSK3β (involved in tau phosphorylation), decreased inflammation, and inhibited apoptotic mechanisms by suppressing the Fas/FasL signaling pathway, cytochrome c release, and caspase 3 activation.

In a mouse model of Alzheimer's disease with chronic cerebral hypoperfusion (APP23 mice plus cerebral chronic hypoperfusion), edaravone treatment (50 mg/kg, i.p.) every other day significantly decreased motor and cognitive deficits, attenuated neuronal loss in the hippocampus, reduced Aβ oligomers and p-tau accumulation, ameliorated white matter lesions in the corpus callosum, enhanced proliferation of oligodendrocyte progenitor cells, attenuated endothelium/astrocyte unit dysfunction, and reduced oxidative stress (Feng et al., 2019; Feng et al., 2021).

Other studies in cell culture and rodent models of Alzheimer's have also shown that edaravone improves cognitive function (Zhou et al., 2013; He et al., 2014; Yang et al., 2015), cell viability (Yan et al., 2012), and mitochondrial function (Yan et al., 2012), while reducing Aβ levels (Shen et al., 2013) and oxidative stress (Yan et al., 2012; Zhou et al., 2013). SH-SY5Y cells pretreated with edaravone prior to Aβ25-35 exposure increased cell survival, decreased apoptosis, and decreased the generation of reactive oxygen species through the activation of the Nrf2/ARE signaling pathway (increased Nrf2 expression and translocation from the cytoplasm to the nucleus, which increased SOD and HO-1)(Zhang et al., 2019).

Cognitive benefits of edaravone have also been demonstrated in rodent models of postoperative cognitive dysfunction (Wang et al., 2016), ischemic stroke (Sun et al., 2015), traumatic brain injury (Ohta et al., 2013), and chronic stress (Jangra et al., 2016).

In a rat model of vascular dementia (chronic cerebral hypoperfusion; CCH), edaravone (5 mg/kg, i.p.) reversed both spatial and fear-memory deficits (Li et al., 2017). Edaravone significantly reduced the level of oxidative stress in the brain by increasing superoxide dismutase (SOD) activity and decreasing levels of reactive oxygen species. Edaravone treatment also restored levels of multiple synaptic proteins in the

hippocampi. In rats that did not undergo CCH, behavioral performance was comparable between edaravone-treated and placebo-treated, suggesting that edaravone may not improve learning and memory in healthy animals with good cognitive function.

In a mouse model of frontotemporal dementia (P301L mice), edaravone treatment, orally via drinking water for 3 months improved reference memory and recognition memory, while alleviating motor deficits (Kelliny et al., 2021). Edaravone treatment also reduced oxidative stress biomarkers (4-hydroxy-2-nonenal and 3-NT adducts), tau phosphorylation, and neuroinflammation.

In a rat model of chemotherapy (cisplatin)-induced cognitive impairment, edaravone treatment (10 mg/kg/week, i.p.) for 7 weeks inhibited cognitive deficits, increased expression of Nrf2 (which regulates expression of antioxidant proteins), and reduced mortality by half (Jangra et al., 2016). Like the study above, the control and edaravone groups without cisplatin had equivalent cognitive scores, suggesting that edaravone may not improve cognitive function in healthy animals.

In a rat model of cognitive impairment (i.c.v. injection of streptozotocin), edaravone treatment (10 mg/kg, orally, once daily) for 28 days ameliorated cognitive impairment, oxidative stress, and inflammatory responses (TNFα, IL1β) (Reeta et al., 2017). Edaravone prevented the streptozotocin-induced increased activity of cholinesterases while normalizing expression of choline acetyltransferase (ChAT) in the cortex and hippocampus, suggesting the treatment may increase acetylcholine levels.

In a mouse model of cognitive impairment induced by AlCl3/D-galactose, edaravone treatment (i.p.) for 15 days improved cognitive deficits, protected hippocampal neurons from oxidative stress (H2O2) and glutamate-induced excitotoxicity, restored antioxidant functions (increased SOD, decreased MDA), and restored the BDNF/TrkB and PI3K/Akt signaling pathways (Wu et al., 2021).

In a young rat model of intermittent-hypoxia-induced oxidative damage and cognitive impairment, edaravone treatment (5 mg/kg, i.p.) for 4 weeks attenuated cognitive impairment and reduced the morphological and structural abnormalities while also increasing the number of mitochondria (Ling et al., 2020). Edaravone treatment also reduced oxidative stress biomarkers, upregulated antioxidant enzymes (MnSOD, catalase), and increased BDNF, phospho-CREB, and anti-apoptotic Bcl-2.

In aged mice undergoing abdominal surgery under general anesthesia, edaravone treatment at high concentrations (33.2 mg/kg, i.p.) significantly attenuated recognition memory and spatial memory impairments (Zhou et al., 2020). Edaravone decreased levels of pro-inflammatory biomarkers, TNF-α, IL-

1β and IL-6, while increasing a synaptic protein, PSD-95 and acetylcholine transmission (decreased AChE activity).

In a rat model of traumatic brain injury, edaravone treatment (3 mg/kg, i.p.) 3 times at 30 minutes, 12 hours, and 24 hours after injury, significantly attenuated neurological impairment and increased neurotropic factor BDNF and TrkB, while decreasing apoptosis in the hippocampus (driven by decreased caspase-3 and Bax-2, increased Bcl-2)(Ding et al., 2019).

APOE4 interactions: Unknown.

Aging and related health concerns: Edaravone treatment improves outcomes for ischemic stroke, intracerebral hemorrhage, and coronary artery bypass surgery by reducing oxidative damage. It is not known if it can prevent age-related diseases.

Types of evidence:

- 2 Cochrane meta-analyses, 1 in ischemic stroke (3 RCTs) and 1 in intracerebral hemorrhage (10 RCTs)
- 3 other meta-analyses, 2 in acute ischemic stroke and intracerebral hemorrhage and 1 in heart surgery patients (7 trials)
- 2 randomized controlled trials in patients with cerebral infarction
- 1 clinical trial in ischemic stroke patients over 80 years old
- 3 laboratory studies, 2 in ischemia-reperfusion injury model and 1 in human neural stem cells

It is unknown whether edaravone prevents age-related diseases, but it has been used extensively for treatment of ischemic stroke and intracerebral hemorrhage. Mechanisms of actions, as in studies above, likely include its free radical scavenging properties as well as its ability to inhibit inflammation and apoptosis (Jiao et al., 2015).

Stroke: Meta-analyses of up to 16 randomized controlled trials have shown that edaravone improves neurological symptoms in patients with acute ischemic stroke or intracerebral hemorrhage (Feng et al., 2011; Yang et al., 2011; Yang et al., 2015). However, the quality of trials in these analyses was generally poor. Higher quality, larger-scale randomized controlled trials are required to confirm these findings.

In a 2021 meta-analysis of 7 RCTs, including 2,069 patients with acute ischemic stroke, edaravone treatment for 3-14 days significantly reduced mortality and improved the neurological impairment (Chen et al., 2021). For the mortality analysis, 3 RCTs with a total of 1,720 patients were included and the pooled relative risk (RR) at 3-month follow-up was 0.55 (95% CI, 0.43-0.7, p<0.01). In the control group, 18.4% of patients died (83 out of 451), while in the edaravone-treated group, 12.1% of patients (153 patients) died. The pooled RR for improvement of neurological impairment at the 3-month follow-up was 1.54 (95% CI, 1.27-1.87, p<0.01) based on data from 4 RCTs (total of 1,778 patients). In the control group, 22.2% of patients showed neurological improvement, while in the edaravone group, 27.2% patients reported neurologic improvement at the 3-month follow-up. Subgroup analysis based on geographic location showed that the RR for improvement of neurological impairment was 1.56 in Asia (3 studies) and 1.32 in Europe (1 study). The subgroup analysis by age showed that the RR was 1.52 for patients over 60 years (3 studies) and 1.80 for patients under 60 (1 study).

In a randomized controlled trial of 130 patients with acute cerebral infarction, edaravone treatment (30 mg, i.v., twice daily) resulted in significantly better stroke scale score (NIHSS) compared to patients receiving conventional treatment (Sun et al., 2019). One week after treatment, NIHSS scores were 18.89±9.84 and 14.45±9.25 for conventional treatment and edaravone treatment groups, respectively. Two weeks after treatment, NIHSS scores were 12.66±7.27 and 7.04±6.34, respectively.

In a clinical study enrolling 96 patients with cerebral infarction, compared to patients receiving conventional therapy, edaravone treatment (30 mg, Sinopharm Guorui Pharmaceutical Co., Ltd.) combined with conventional therapy for 2 weeks lowered the stroke scale score (NIHSS), improved activities of daily living score, and decreased serum inflammation biomarkers, TNF-α and IL-8 (Li et al., 2020). Conventional therapy consisted of oxygen therapy, sedation, antiplatelet aggregation, and other measures that decrease blood pressure and intracranial pressure, promote brain metabolism and blood circulation to remove blood stasis, and manage water and electrolyte imbalance.

In ischemic stroke patients over 80 years old, treatment with edaravone in combination with recombinant tissue plasminogen activator (tPA) improved clinical outcomes 3 months after the stroke (Kono et al., 2013).

The mechanism of protection in ischemic stroke is likely through the reduction of free radicals, which are produced by the peroxidation of unsaturated fat in phospholipids within the cell membrane, damaging the cells and promoting secondary brain tissue damage (Chen et al., 2021).

Coronary artery bypass surgery: A meta-analysis of 7 clinical trials in patients undergoing coronary artery bypass surgery showed that edaravone treatment (60 mg/day for 14 days) decreased the proportion of patients with marked heart damage compared to controls (Zheng et al., 2015). Edaravone-treated patients had decreased markers of myocardial damage (i.e., creatine kinase-MB, cardiac troponin 1, and MDA, an oxidative stress marker).

Preclinical studies: In rodent models of ischemia-reperfusion injury, edaravone treatment reduced neuronal (Wen et al., 2006; Ren et al., 2019). and cardiomyocyte death (Watanabe et al., 2007). Edaravone also protected human neural stem cells from irradiation (Ishii et al., 2007).

In a rat model of intracerebral hemorrhage, a combination of pharmacologically-induced hypothermia (with neurotensin receptor agonist HPI-201) and edaravone (10 mg/kg) significantly prevented brain edema, blood-brain-barrier permeability, and expression of inflammatory cytokines (IL-1β, IL-6, TNF-α) (Zhu et al., 2015).

In a strain of mice (EL mice) that is highly susceptible to convulsive seizures, edaravone treatment (10 mg/kg/day, i.p.) for 7 days significantly increased antioxidant potency (GSH/GSSG ratio) and reduced seizure susceptibility (Baba et al., 2016).

Safety: Numerous meta-analyses in stroke, intracerebral hemorrhage, and ALS have shown that incidences of adverse events with edaravone are not significantly different from placebo. However, thrombotic events are associated with chronic intravenous access.

Types of evidence:

- 4 meta-analyses or systematic reviews based on 3-16 RCTs in patients with ischemic stroke or intracerebral hemorrhage
- 1 meta-analysis and systematic review based on 3 RCTs in ALS patients
- 3 double-blind RCTs, 1 in ALS patients, 1 in surgery patients, and 1 in acute ischemic stroke patients
- 2 open-label clinical studies in ALS patients
- 1 phase 3 safety trial testing an investigational oral edaravone, MT-1186 in ALS patients
- 1 phase I randomized single-blind placebo-controlled study in healthy subjects
- 1 randomized open-label crossover trial in healthy subjects to test a sublingual formulation of edaravone

- 1 open-label pharmacokinetic study in people with hepatic impairment
- 2 retrospective studies, 1 in ALS patients and 1 in patients with carbon monoxide poisoning
- 1 small study in pediatric cerebral ischemia patients
- 1 phase I clinical study in healthy volunteers

Stroke and intracerebral hemorrhage patients: Four meta-analyses in patients with acute ischemic stroke or intracerebral hemorrhage have reported that adverse events with edaravone are common (9%) but mild. In two Cochrane meta-analyses, one in acute ischemic stroke patients (Feng et al., 2011) and the other in patients with intracerebral hemorrhage (Yang et al., 2011), no differences in adverse events were found between edaravone-treated versus non-treated groups. Edaravone treatment was also not associated with increased or decreased numbers of death during treatment (RR 0.62, 95% CI, 0.11 to 3.50) or at 3-month follow-up (RR 0.93, 95% CI, 0.20 to 4.32). In another meta-analysis, which included patients with acute ischemic stroke (16 RCTs) and intracerebral hemorrhage (14 RCTs), the most common adverse event was mild impairment of kidney function, reported in 3.25% of patients receiving edaravone versus 1.49% in controls (Yang et al., 2015). One patient receiving edaravone had acute renal failure so edaravone may not be recommended for people with renal dysfunction. The incidence of mild impairment of liver function was similar in edaravone-treated (3.18%) versus controls (3.23%)(Yang et al., 2015). In the latest 2021 meta-analysis of 7 RCTs including a total of 2.069 patients with acute ischemic stroke, the RR for the incidence of any treatment-related adverse events was 0.83 (95% CI, 0.51 to 1.34, p=0.43) and the difference between edaravone treatment and placebo or no intervention was not statistically significant (Chen et al., 2021). In the edaravone-treated group, various adverse effects were observed in 12.4% of patients (28 out of 240). There were no significant differences between edaravone and control groups in terms of occurrence of nausea (RR=1.31, 95% CI, 0.33 to 5.29), skin rash (RR=1.05, 95% CI, 0.33 to 3.36) and abnormal liver function (RR=0.65, 95% CI, 0.22 to 1.91). In the evaluated studies, 2 severe treatment-related adverse events were reported, which was a gout flare reported twice in the same patient.

ALS patients: Edaravone was approved in the US based on results from a phase III study in ALS patients that were published in May 2017. In a phase 3 double-blind RCT, 137 early-stage ALS patients were recruited and received edaravone (60 mg, i.v.) or saline for 24 weeks (6 cycles of 2 weeks on and 2 weeks off)(Writing Group, Edaravone ALS 19 Study Group, 2017). Edaravone-treated patients experienced a significantly smaller decline in functional impairment (ALSFRS-R score) compared to those receiving placebo. The number of patients reporting at least one adverse event did not differ between edaravone and control groups. Incidents of adverse events and severe adverse events were also comparable between the two groups. Adverse events were reported in 58 (84%) patients

receiving edaravone and 57 (84%) patients receiving placebo. Eleven (16%) patients taking edaravone and 16 (24%) taking placebo had severe adverse events, which included dysphagia (difficulty swallowing; 12% in edaravone, 12% in placebo) and respiratory disorder (3% in edaravone and 3% in placebo). One (1%) patient receiving edaravone and 4 (6%) patients receiving placebo had adverse events (1 dysphagia in edaravone group and 1 dyspnea, 2 respiratory disorder, and 1 rash in the placebo group) that led to withdrawal from the trial. No deaths were reported during the study. Adverse events with incidence of 10% or more were contusion, constipation, and dysphagia in both groups, and dermatitis contact in edaravone group. The only severe adverse events+ with incidence of over 5% was dysphagia (difficulty swallowing) observed in both groups. No changes in laboratory and sensory tests were observed between groups. Two (3%) of 69 patients receiving edaravone had adverse drug reactions (abdominal discomfort, eczema, and abnormal liver function test) and 7% of controls had adverse reactions (dizziness, constipation, rash, chondrocalcinosis pyrophosphate, increased blood bilirubin, increased blood creatine phosphokinase, and abnormal liver function test).

In a systematic review and meta-analysis of 3 RCTs including a total of 367 ALS patients, edaravone treatment (60 mg/day, i.v.) for 24 weeks resulted in no differences in the frequency of adverse events (OR=1.22, 95% CI, 0.68 to 2.19) or serious adverse events (OR=0.71, 95% CI, 0.43 to 1.19) compared to those receiving placebo (Luo et al., 2019). All adverse events were mild to moderate and considered by investigators to be unrelated to the study drug. In both edaravone and placebo groups, the most frequently seen treatment-emergent severe adverse events were dysphagia, respiratory disorder, speech disorder, and pneumonia aspiration, and these were not considered to be associated with edaravone, but instead attributed to ALS disease progression.

A double-blind randomized controlled trial in ALS patients also showed that the incidence of adverse events in edaravone-treated (89.2%) versus placebo-treated (88.5%) groups were comparable (Abe et al., 2014).

In a retrospective analysis of 57 consecutive ALS patients, of whom 27 were treated with edaravone and 30 were not, edaravone treatment (14 days followed by 2-week drug-free, subsequently 5 days/week for 2 weeks drug, followed by 2-week drug-free) for a mean treatment duration of 8.8 months resulted in 10 out of 27 patients discontinuing edaravone (Okada et al., 2018). Only one patient stopped edaravone treatment due to a side effect, which was renal dysfunction due to drug interactions with antibiotics. Other reasons for discontinuation included vein inflammation, worsening of ALS disease, difficulty with vascular access, and patient request.

In an open-label clinical study of 31 ALS patients in North-Eastern Italy, edaravone treatment (Avone®, a commercially available edaravone bioequivalent of Radicut®) for 2 weeks each month for 6 months was well-tolerated (Fortuna et al., 2019). One patient died before the second treatment cycle due to unexplained causes and 6 patients discontinued therapy within 6 months, due to deep venous thrombosis (2 patients, common in ALS patients), a suspected acute lung injury (1 patient), and lack of effects (3 patients). Minor adverse events included mild and transient dizziness in 1 patient and burning sensation at the injection site in a few cases.

Postmarketing data in the US show that 3,007 ALS patients were prescribed with edaravone (Radicava®) and the most commonly reported adverse events were asthenia, fatigue, gait disturbance, disease progression, muscular weakness, fall, and dyspnea (Jackson et al., 2019).

In an editorial, caveats in the interpretation of the phase 3 ALS trials are discussed, and the author proposes that the efficacy of edaravone may be overestimated because of the harm that can be imposed in long-term intravenous placebo administration (Turnbull, 2018). The author pointed out that in the phase 3 trial, the rate of ALSFRS decline showed a sharp downward inflection after randomization and argued that intravenous edaravone infusions proved superior to intravenous placebo infusions, but it did not indicate that the treatment is better than no intervention. Thrombotic side effects are associated with chronic intravenous access, and these are often asymptomatic. One argument against the above editorial is that in a retrospective analysis of ALS patients, of whom 27 were treated with edaravone and 30 were not given treatment, edaravone infusions (14 days followed by 2-week drug-free, subsequently 5 days/week for 2 weeks drug, followed by 2-week drug-free) for a mean treatment duration of 8.8 months resulted in slower progression and better prognosis compared to those who did not receive edaravone (Okada et al., 2018). The inconsistencies in efficacies across studies could be partly explained by differences in the genetics of ALS in Japanese vs. European people (SOD1 mutations and C9Orf72 expansions are more common in Japanese and European people, respectively)(Zou et al., 2017). These genetic differences may affect oxidative stress pathways differently, making responses to edaravone, including adverse events, dissimilar across populations.

In a global phase 3 safety study enrolling 185 ALS patients in the US, Canada, Europe, and Japan, treatment with an investigational oral edaravone, MT-1186 (Mitsubishi Tanabe Pharma Corporation), for 24 weeks did not result in any serious treatment-emergent adverse events considered by the investigators to be treatment-related (news release). Common treatment-emergent adverse events were muscular weakness (16.2%), fall (15.7%), fatigue (7.6%), back pain (7.0%), constipation (7.0%), headache (5.9%), and dyspnea (5.4%). Eleven patients (5.9%) discontinued treatment due to adverse

events, and 2 of them were related to the study drug. There were 6 deaths during the 24-week period and none of the deaths were related to the study drug (respiratory failure, pneumonia, and suicide). This trial is ongoing and will continue to evaluate MT-1186 for up to 96 weeks.

Patients undergoing surgery: In a double-blind RCT in 80 elderly patients undergoing hip joint replacement surgery, edaravone treatment (0.5 mg/kg, i.v.) 10 minutes prior to beginning of surgery did not result in any complications, including liver and kidney function impairment (Zhang et al., 2020).

Patients with hepatic impairment: In an open-label, single-dose study of pharmacokinetics and safety, 20 people with mild, moderate, or severe hepatic impairment received a single intravenous infusion of edaravone (30 mg over 60 minutes)(Nakamaru et al., 2020). One adverse event of sinus bradycardia, moderate in severity, was observed in a subject with normal hepatic functioning and considered possibly related to edaravone. Other treatment-emergent adverse events including flank pain and chest pain were considered not be related to the study drug. No treatment-emergent severe adverse events were reported during the study. Laboratory parameters, vital signs, ECG, and physical examination did not show clinically significant abnormalities. People with mild, moderate, or severe hepatic impairment did not have clinically significant differences in the pharmacokinetics of edaravone compared to people with normal hepatic functioning. Thus, dosage adjustments of edaravone are unlikely to be needed based on hepatic impairment.

Patients with carbon monoxide poisoning: A small clinical study including patients who had carbon monoxide poisoning reported that no patients presented with complications from edaravone treatment (Mori et al., 2015).

Healthy people: In a phase I clinical study in healthy volunteers (n=30), edaravone doses of up to 60 mg/day for 5 days were well-tolerated and no symptomatic adverse events were observed (Li et al., 2012). However, some abnormalities in laboratory test results were reported, including increased alanine transaminase (liver function) and triglyceride levels, and decreased white blood cell counts and creatinine levels (kidney function). These changes were judged to be small in magnitude and tolerable, and all abnormal indices returned to normal levels within 7 days.

In a phase I randomized, single-blind, placebo-controlled, 3-way crossover study of 27 healthy Japanese male volunteers, 2 doses of edaravone (60 or 300 mg, i.v.) were tested (Shimizu et al., 2021). Even at a supratherapeutic dose of 300 mg of edaravone, no clinically meaningful QT prolongation was observed, and there were no clinically relevant cardiac effects. Mean values for heart rate, PR interval, and QRS

duration were similar between edaravone and placebo. A total of 3 treatment-emergent adverse events were reported in 3 subjects: pharyngitis in the 60-mg edaravone group, headache in the placebo group, and gastroenteritis in the 300-mg edaravone group. All of these resolved, and none were considered drug-related. There were no clinically significant findings on vital signs, ECG, laboratory tests, and physical examination.

In a randomized, open-label, 2-way crossover trial in 11 healthy male volunteers, bioavailability and tolerability of sublingual edaravone (30 mg) was evaluated against an intravenous dose, and 2 cases of adverse events were reported during the study (Wang et al., 2018). One subject experienced hypotension shortly after the sublingual dose, and another subject reported discomfort on the tongue for 2 hours during the intravenous dosing period. These adverse events were considered by the investigator as possibly not related to the study drug. No clinically significant changes in vital signs, laboratory tests, ECG, or physical examination were found.

Drug interactions: Edaravone is metabolized by multiple uridine diphosphate-glucuronosyltransferase (UGT) enzymes (Drugs.com). Specific drugs known to interact with edaravone are not listed.

Sources and dosing: Edaravone is used for treating acute ischemic stroke and ALS in Japan. Sources of edaravone include Radicut® (MCI-186) by Mitsubishi Tanabe Pharma in Japan and Arone® by Edinburgh Pharmaceuticals in India. In 2017, edaravone was approved for the treatment of ALS in the US and is sold under the brand name Radicava™.

Edaravone is currently administered intravenously. The most commonly used dose is 30 mg twice daily in adults. Treatment duration in clinical studies range from 3-28 days for acute ischemic stroke, hemorrhagic stroke, and heart surgery, and for up to 24 weeks for ALS patients. Oral formulations of edaravone are being tested in clinical studies (e.g., Mitsubishi Tanabe Pharma's MT-1186 and Treeway's TW001, discussed below).

Research underway: Based on ClinicalTrials.gov, as of February 2022, there are 16 ongoing clinical trials testing edaravone in patients with ALS, stroke, intracerebral hemorrhage, and alcohol-induced brain injury (ClinicalTrials.gov).

Oral formulations of edaravone are under clinical development. In October 2019, Mitsubishi Tanabe Pharma's MT-1186, an oral suspension of edaravone, received Fast Track designation from the FDA. In

December 2021, results of a global phase 3 safety study were presented at the Motor Neurone Disease Association virtual 32nd International Symposium on ALS/MND (news release).

A biotech company Treeway B.V. has also developed an oral formulation of edaravone (TW001). In October 2021, Treeway and Ferrer (international pharmaceutical company focused on pulmonary and neurological diseases) entered into a license agreement for the development and commercialization of TW001 (now called FNP122) for ALS in Europe and some Asian countries (press release). In November 2021, the first patient was enrolled for the phase 3 clinical trial of FNP122 in ALS (press release). ADDF is funding a phase 2a clinical trial to test oral edaravone in Alzheimer's patients (ADDF news room).

In a randomized, open-label, 2-way crossover trial in 11 healthy male volunteers, bioavailability and tolerability of sublingual edaravone (30 mg) was evaluated, and the sublingual tablet produced a 91.94% bioavailability compared to the intravenous dose (Wang et al., 2018). Cmax with the sublingual dose was approximately 17% lower and the Tmax was significantly longer. The authors noted that the pharmacokinetic differences can be addressed by altering the strength of the sublingual tablet.

Search terms:

Pubmed, Google: Edaravone, Radicut, MCI-186, TW001, MT-1186

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