NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2023

Edaravone for treating amyotrophic lateral sclerosis

Company/Developer	Ferrer Internacional, S.A.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34567	NICE ID: 11869	UKPS ID: 668257

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Daily oral edaravone is currently in clinical development for amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease (MND). ALS is a rare, life-limiting disease that causes the deterioration of nerve cells in the brain and spinal cord, which control voluntary movements such as walking and breathing. The gradual decline of nerve cells causes a loss of muscle function, difficulty moving and eventually paralysis, problems breathing without ventilatory support and death. There is a lack of effective treatments for ALS.

Edaravone is thought to be a potent anti-oxidant and may slow the progression of ALS by protecting nerve cells through 'scavenging' unstable molecules called reactive oxygen species, which are linked to nerve damage in patients with ALS. If licensed, oral edaravone will offer an additional treatment option for patients with ALS who currently have few effective therapies available.

Proposed Indication

Treatment for adult patients (aged 18-80) with amyotrophic lateral sclerosis (ALS).[1]

Technology

Description

Edaravone (FNP122) is a free radical scavenger that scavenges and suppresses the generation of hydroxyl radicals and peroxynitrite radicals.[2] The exact mechanism of action of edaravone in ALS has not been fully elucidated; however, edaravone is thought to mediate therapeutic effects via its antioxidant properties.[2] It delays the disease progression by limiting the extent of neuronal damage or death.[2]

Daily oral edaravone is currently in clinical development for ALS in adult patients.[1] In the phase III clinical trial (NCT05178810; ADORE), edaravone is administered orally at doses of 100mg once daily.[1]

Key Innovation

Considering the debilitating and life-limiting nature of ALS, few treatment options are available. Medical care focuses on supportive and palliative interventions to increase the patient's quality of life.[3] One disease modifying treatment, riluzole, which is administered orally, is approved in the UK and has shown to have a modest effect on survival in clinical trials. Previous evidence investigating the efficacy of edaravone (via intravenous delivery) in combination with riluzole has shown favourable effects which provides a significant benefit for patients with ALS.[4]

Edaravone acts as an antioxidant, a molecule that can prevent damage to nerve cells caused by oxygen-containing molecules. It also blocks the clumping together of superoxide dismutase in the nerves to reduce inflammation.[4] If licensed, edaravone will offer an additional treatment option for patients with ALS who currently have few effective disease modifying therapies available.

Regulatory & Development Status

Oral edaravone does not currently have marketing authorisation in the EU/UK for any indication.

Oral edaravone is currently in phase II clinical development for the treatment of Alzheimer disease.[5]

Oral edaravone has orphan drug designation in the EU in 2014 for the treatment of ALS.[6]

Patient Group

Disease Area and Clinical Need

ALS is a rare, progressive and fatal neurodegenerative condition.[7] ALS is characterised by the progressive degeneration and death of upper motor neurons (nerves) in the brain and spinal cord and lower motor neurons, located in the spinal cord and connected to voluntary muscles in the face, throat, arms, chest and legs.[8] The degeneration of motor neurons and interruption of messages to voluntary muscles causes the muscles to increase in tone or atrophy.[8] ALS symptoms impact individuals differently but usually occur gradually and result in difficulties moving the hands, arms, legs, and feet, and can affect a person's ability to speak, swallow, and breathe.[9] Early symptoms may include tripping, dropping things, fatigue in arms and legs, slurred speech, muscle cramps or twitches and uncontrollable periods of laughing or crying.[9] Eventually, the end stages of ALS lead to paralysis, and as the muscles in the person's chest and diaphragm weaken, they will require permanent mechanical ventilatory support to breathe.[8] The exact cause of ALS

is not yet fully understood but is thought to involve complex interactions between genetic and molecular pathways, including, but not limited to, oxidative stress and neuro-inflammation.[7]

ALS is the most common form of MND in the UK, accounting for approximately 60-70% of the total MND cases.[10] The incidence of ALS ranges from 1.8 to 2.2 per 100,000 population, and the prevalence ranges from 4.0 to 4.7 per 100,000 population in the UK.[11] In England, 2021-22, there were 4,406 finished consultant episodes (FCE) and 2,694 admissions for MND (ICD-10 code G12.2), resulting in 21,826 FCE bed days and 1,029 day cases.[12]

Recommended Treatment Options

Riluzole is the only recommended treatment option by the National Institute for Health and Care Excellence (NICE) for the treatment of ALS.[11] Other recommended treatments are supportive care only.[3]

Clinical Trial Information

Trial	**ADORE**, NCT05178810, EudraCT 2020-003376-40; A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of FAB122 in Patients With Amyotrophic Lateral Sclerosis **Phase III –** Active, not recruiting **Location(s):** Ten EU countries and the UK **Primary completion date:** June 2024
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo controlled
Population	N=300; Male and female patients aged between 18 -80 years with diagnosis of definite, probable, probable laboratory supported or possible ALS as based on the El Escorial and the revised Airlie House diagnostic criteria for ALS.
Intervention(s)	Once daily oral dose of 100mg edaravone
Comparator(s)	Placebo
Outcome(s)	Primary outcome: Change from baseline in revised Amyotrophic Lateral Sclerosis Functioning Rating Scale (ALSFRS-R) [Time frame: 48 weeks]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of oral edaravone was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sodium phenylbutyrate–ursodoxicoltaurine for treating amyotrophic lateral sclerosis (GID-TA11264). Expected date of issue to be confirmed.

- NICE technology appraisal in development. Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations (GID-HST10050). Expected July 2024.
- NICE technology appraisal in development. Masitinib with riluzole for treating amyotrophic lateral sclerosis (GID-TA11071). Expected date of issue to be confirmed.
- NICE technology appraisal. Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20). January 2001.
- NICE clinical guideline. Motor neurone disease: assessment and management (NG42). February 2016. Updated: July 2019.
- NICE quality standard. Motor neurone disease (QS126). July 2016. Last updated: July 2019.
- NICE interventional procedure guidance. Intramuscular diaphragm stimulation for ventilator dependent chronic respiratory failure caused by motor neurone disease (IPG593). September 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised rehabilitation for patients with highly complex needs (All ages). D02/S/a.

Other Guidance

- Motor neuron disease association (MNDA). Motor neurone disease: a guide for GPs and primary care teams. 2018.[13]

Additional Information

References

1 ClinicalTrials.gov. *Study to Investigate the Efficacy and Safety of FAB122 (Daily Oral Edaravone) in Patients With Amyotrophic Lateral Sclerosis. Trial ID: NCT05178810.* 2021. Available from: https://ClinicalTrials.gov/show/NCT05178810 [Accessed 15 March 2023].

2 Drugbank. *Edaravone*. 2016. Available from: https://go.drugbank.com/drugs/DB12243 [Accessed 04 March 2023].

3 National Institute for Health and Care Excellence (NICE). *Motor neurone disease: assessment and management*. 2016. Available from: https://www.nice.org.uk/guidance/ng42/chapter/Recommendations [Accessed 07 March 2023].

4 European Medicines Agency (EMA). *EU/3/15/1510: Orphan designation for the treatment of amyotrophic lateral sclerosis*. 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151510 [Accessed 03 March 2023].

5 ClinicalTrials.gov. *Edaravone | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Edaravone&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=

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6 European Medicines Agency (EMA). *EU/3/14/1399: Orphan designation for the treatment of amyotrophic lateral sclerosis*. 2014. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-14-1399 [Accessed 29 March 2023].

7 European Medicines Agency (EMA). *Withdrawal assessment report Radicava* 2019. Available from: https://www.ema.europa.eu/en/documents/withdrawal-report/withdrawal-assessment-report-radicava_en.pdf.

8 National Organisation of Rare Disorders (NORD). *Amyotrophic Lateral Sclerosis*. 2023. Available from: https://rarediseases.org/rare-diseases/amyotrophic-lateral-sclerosis/?filter=ovr-ds-resources [Accessed 14 March 2023].

9 ALS Association. *ALS Symptoms and Diagnosis*. Available from: https://www.als.org/understanding-als/symptoms-diagnosis [Accessed 14 March 2023].

10 NHS The Leeds Teaching Hospitals. *Different types of MND*. Available from: https://www.leedsth.nhs.uk/a-z-of-services/leeds-motor-neurone-disease-mnd-care-centre/your-condition-and-treatment/different-types-of-mnd/ [Accessed 15 March 2023].

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12 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 07 March 2023].

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.