Health Technology Briefing
May 2026

Ulefnersen for treating amyotrophic lateral sclerosis

Company/Developer	Otsuka Pharmaceutical Co Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 31266	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase I-III clinical development.

Summary

Ulefnersen is currently being developed for the treatment of patients with amyotrophic lateral sclerosis (ALS) who have alterations in the fused in sarcoma (FUS) gene. ALS is a neurological disorder that affects motor neurons. Motor neurons are the nerve cells in the brain and spinal cord that control voluntary muscle movement and breathing. ALS is a form of motor neurone disease in which the nerves that control movement gradually stop working, leading to muscle weakness, stiffness, and wasting, affecting the ability to walk, speak, eat, and breathe. Symptoms worsen over time, and the condition is life-shortening. FUS-related ALS is a rare but more aggressive form of the disease that often occurs earlier in life and progresses quickly. There are currently no specific treatments available for people with FUS-related ALS, highlighting a significant unmet clinical need.

Ulefnersen is a type of drug designed to target the genetic cause of FUS-related ALS (FUS-ALS). It works by attaching to the ribonucleic acid (RNA) produced from the FUS gene, reducing the amount of harmful FUS protein in nerve cells. By lowering this protein, ulefnersen may delay, halt, or even reverse disease progression in FUS-ALS patients. Ulefnersen is given as an injection into the fluid around the brain and spinal cord (lumbar intrathecal injection). If approved (licensed), ulefnersen would provide a treatment option for patients with FUS-ALS.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Treatment of amyotrophic lateral sclerosis (ALS) patients with fused in sarcoma mutations (FUS) [FUS-ALS].[1]

Technology

Description

Ulefnersen (Jacifusen, ION363) is a short single-stranded DNA molecule known as an antisense oligonucleotide. It is designed to specifically target the FUS pre-messenger ribonucleic acid (mRNA), reducing FUS mRNA and thereby preventing production of the FUS protein, with reduction of toxic mutant FUS protein levels.[2,3] By targeting an intronic sequence, ulefnersen is expected to decrease FUS toxicity in patients with FUS-ALS.[4]

Ulefnersen is currently in clinical development for the treatment of patients with FUS-ALS. In the ongoing phase III clinical trial (FUSION; NCT04768972), ulefnersen is administered to patients by lumbar intrathecal bolus injection every 12 weeks, with an additional loading dose at 4 weeks, over a 60-week double-blind treatment period.[1,3]

Key Innovation

Mutations in FUS are associated with the most aggressive, early-onset forms of ALS.[4] Although there are no specific FUS-ALS treatments, currently approved treatments for ALS provide a modest increase in survival (2 to 3 months) without noticeable improvement in strength or disability.[5] Preclinical studies and postmortem analyses demonstrate reduced FUS protein levels and decreased FUS pathology in CNS tissues following ulefnersen.[4] The first-in-human, open-label, investigator-initiated expanded-access case series of ulefnersen in individuals with FUS-ALS demonstrated substantial target engagement and neurofilament light chain (NfL) biomarker reductions, with heterogenous clinical trajectories observed across participants.[6] The reduction of toxic mutant FUS protein may delay, halt, or even reverse disease progression in FUS-ALS patients.[5]

If licensed, ulefnersen would provide a disease-modifying treatment option for patients with FUS-ALS who currently have no approved targeted therapies.

Regulatory & Development Status

Ulefnersen does not currently have Marketing Authorisation in the EU/UK for any indication.

Ulefnersen is not currently in any other phase II or III clinical trial.

Ulefnersen has received the following designations:

- An EMA Orphan designation for the treatment of ALS on the 22nd May 2023.[7]
- An FDA Orphan designation for the treatment of ALS on the 15th August 2023.[8]

Patient Group

Disease Area and Clinical Need

ALS is a neurological disorder that affects motor neurons. Motor neurons are the nerve cells in the brain and spinal cord that control voluntary muscle movement and breathing.[9] ALS is the most common form of motor neurone disease (MND).[10] In MND, messages from the motor neurones gradually stop reaching the muscles. This leads the muscles to weaken, stiffen and waste, which can affect the ability to walk, talk, eat,

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drink and breathe. ALS is characterised by symptoms such as weakness and wasting in the limbs, muscle stiffness and cramps. Symptoms also progress at varying speeds, which makes the course of the disease difficult to predict. Although the disease will progress, symptoms can be managed to help achieve the best possible quality of life.[10] Whilst FUS-ALS is a very rare form of ALS, it is the most common cause of ALS in childhood and early adulthood when it typically presents with fast progression rates and a more aggressive disease course.[3] MND can affect adults of any age but is more likely to affect people over 50 years. It is life-shortening and currently has no cure.[10]

MND affects up to 5,000 adults in the UK at any one time. There is a 1 in 300 risk of getting MND across a lifetime.[10] Nearly 90 percent of patients with MND have the mixed ALS form of the disease.[11] FUS mutations account for approximately 1-2% of all ALS cases.[3] Given these estimates at any time 45-90 patients in the UK population might have FUS-ALS. Life expectancy is usually two to five years from the onset of symptoms.[10] In England 2024-25, there were 5,408 finished consultant episodes (FCEs) and 3,415 hospital admissions for MND (ICD-10 code G12.2), resulting in 25,571 FCE bed days and 1,666 day-cases.[12]

Recommended Treatment Options

There are currently no treatment recommendations targeting FUS-ALS specifically. The National Institute for Health and Care Excellence (NICE) currently recommends riluzole for the treatment of motor neurone disease for individuals with ALS.[13]

Clinical Trial Information

Trial	**FUSION**, NCT04768972, 2020-005522-28; A Phase 1-3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ION363 in Amyotrophic Lateral Sclerosis Patients With Fused in Sarcoma Mutations (FUS-ALS) **Phase III**: Active not recruiting **Locations:** UK, USA, Canada, Japan, 8 EU countries and other countries **Primary Completion Date:** June 2026
Trial Design	Randomised, parallel assignment, double blind
Population	N=89 (actual); subjects with ALS with fused in sarcoma mutations (FUS-ALS); aged 10 years and older
Intervention(s)	Ulefnersen administered by lumbar intrathecal bolus injection every 12 weeks, with an additional loading dose at 4 weeks, over a 60-week double-blind treatment period
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: Change from Baseline (Day 1) through Study Day 505 in Part 1 in functional impairment See trial record for full list of outcomes.
Results (efficacy)	-

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Results (safety)	-

Estimated Cost

The cost of ulefnersen is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Edaravone for treating amyotrophic lateral sclerosis [TSID11869] (GID-TA11362). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Masitinib with riluzole for treating amyotrophic lateral sclerosis [ID6257] (GID-TA11071). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pegcetacoplan for amyotrophic lateral sclerosis [TS ID 10594] (GID-TA11310). 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. Last updated July 2019.
- NICE quality standard. Motor neurone disease (QS126). July 2016.

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 Neurone Disease Association. Motor neurone disease: a guide for GPs and primary care teams. 2022.[14]

Additional Information

Otsuka Pharmaceutical Co Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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1 ClinicalTrials.gov. *FUSION: A Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of ION363 in Amyotrophic Lateral Sclerosis Participants With Fused in Sarcoma Mutations (FUS-ALS). Trial ID: NCT04768972*. 2026. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT04768972 [Accessed 12 March 2026].

2 PR Newswire. *Ionis initiates Phase 3 trial of novel antisense medicine to treat leading cause of juvenile-onset ALS*. 2021. Available from: https://www.prnewswire.com/news-releases/ionis-initiates-phase-3-trial-of-novel-antisense-medicine-to-treat-leading-cause-of-juvenile-onset-als-301261713.html [Accessed 12 March 2026].

3 MND Research Blog. *Silence is golden: A new clinical trial for FUS-ALS* 2022. Available from: https://mndresearch.blog/2022/02/14/silence-is-golden-a-new-clinical-trial-for-fus-als/?_gl=1*7ichkx*_gcl_au*MTc2NjQzNTA0MS4xNzczMzI4MTQ0*_ga*MTYyMTI2MTEwLjE3NzMzMjgxNDQ.*_ga_6S1ZJSGWM8*czE3NzMzMjgxNDMkbzEkZzEkdDE3NzMzMjg4NzAkajYwJGwwJGgw*_ga_3D3SSHZ8RB*czE3NzMzMjgxNDMkbzEkZzEkdDE3NzMzMjg4NzAkajYwJGwwJGgw [Accessed 12 March 2026].

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12 National Health Service Digital. *Hospital Admitted Patient Care Activity, Diagnosis 2024-25*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2024-25 [Accessed 28 January 2026].

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