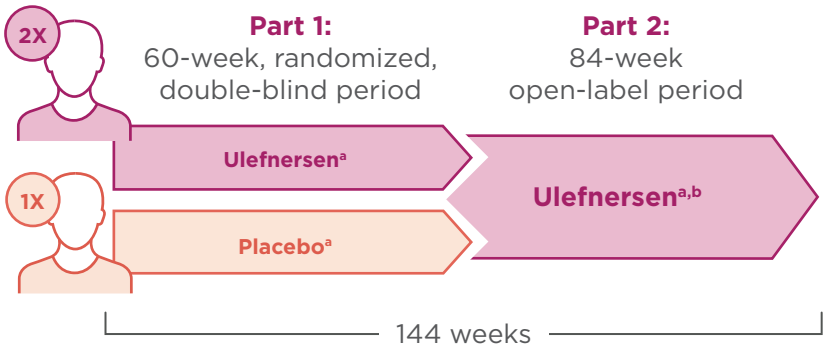
The FUSION Study Is Evaluating Ulefnersen, an Investigational RNA-Targeted Medicine, for People With FUS-ALS[1,2]

FUSION

The Phase 1-3, double-blind, placebo-controlled clinical trial is currently underway[1,2]

Study objective:

To determine if an investigational RNA-targeted antisense medicine, ulefnersen, is safe and capable of halting, reversing, or slowing deterioration based on clinical functioning and biomarkers in people with FUS-ALS.[1,2]



This is a multicenter, two-part study of ulefnersen. **Part 1** will consist of participants who will be randomized in a 2:1 ratio to receive a multidose regimen of ulefnersen or placebo for a period of 60 weeks with a 12-week follow-up, followed by **Part 2,** which will be an open-label period where all participants will receive ulefnersen for a period of 84 weeks.[2]

Select inclusion/exclusion criteria[1,c]:

- People aged ≥12 years with signs or symptoms consistent with ALS
- Confirmed genetic mutation in *FUS*[d]
- Upright SVC[e] ≥50% of predicted value
- People who require permanent ventilation[f] and/or tracheostomy are excluded
- People who have any known ALS-associated mutations, other than *FUS* are excluded

Table: Key Clinical Endpoints[1]

Primary Endpoint	Change From Baseline (Day 1) Through Study Day 505 in Part 1 in Functional Impairment[g]
Secondary Endpoints	Change From Baseline in ALSSQOL-R Change From Baseline in In-Clinic ALSFRS-R Survival Change From Baseline in In-Clinic SVC Change From Baseline in HHD Change From Baseline in CSF NfL Concentration

For more study information scan here:

Ulefnersen has not been evaluated for safety and efficacy by any regulatory authorities, and ulefnersen is not indicated for the treatment of any disease.

[a]Administered by lumbar intrathecal bolus injection.[1] [b]Participants who complete Part 2 will have the opportunity to enroll in Part 3, an open-label extension with continued access to ulefnersen and monitoring until ulefnersen receives marketing authorization or its development is discontinued.[1] [c]This is not an exhaustive list. [d]By a certified, CE-marked, or equivalent testing laboratory, mutations must be reviewed and approved by a variant classification committee.[1] [e]As adjusted for sex, age, and height. [f]More than 22 hours of mechanical ventilation (invasive or noninvasive) per day for >21 consecutive days.[1] [g]Functional impairment to be measured by joint rank analysis of the combined assessment of function and survival.[1]

ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSSQOL-R, Revised Amyotrophic Lateral Sclerosis Specific Quality of Life; CSF, cerebrospinal fluid; FUS-ALS, Fused in Sarcoma amyotrophic lateral sclerosis; HHD, handheld dynamometry; NfL, neurofilament light; SVC, slow vital capacity.

1. ClinicalTrials.gov. Accessed February 19, 2024. https://clinicaltrials.gov/ct2/show/NCT04768972/ 2. Ionis Pharmaceuticals. Data on file.

IONIS

Ulefnersen Is an Investigational RNA-Targeted Medicine (RTM) That Has Been Designed to Reduce CNS Expression of FUS[1-4]

FUSION

Proposed Ulefnersen-Mediated Downregulation of FUS[1-4]

Ulefnersen lowered levels of wild-type and mutant FUS in the CNS, which resulted in a marked reduction in the burden of FUS aggregates, a pathological hallmark of the disease, in animal models and a compassionate use authorization in a single human patient.[4]

Ulefnersen has not been evaluated for safety and efficacy by any regulatory authorities, and ulefnersen is not indicated for the treatment of any disease.

For more information or questions about participating sites, please contact us at **ionisNCT04768972study@clinicaltrialmedia.com** or **844-421-0104.**[5]

LEADING THE RNA REVOLUTION

in the treatment of neurologic disease

With a history of major breakthroughs in RNA-targeted technology, Ionis' robust pipeline is filled with potential.

CNS, central nervous system; dsDNA, double-stranded DNA; FUS, Fused in Sarcoma; mRNA, messenger RNA.

1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol.* 2021;61:831-852. 2. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed February 18, 2024. https://www.ionispharma.com/ionis-technology/antisense-pipeline/ 3. Dhuri K, et al. *J Clin Med.* 2020;9(6):2004. 4. Korobeynikov VA, et al. *Nat Med.* 2022;28(1):104-116. 5. ClinicalTrials.gov. Accessed February 19, 2024. https://clinicaltrials.gov/ct2/show/NCT04768972/

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