# Ionis announces positive topline results from Phase 3 FUSION study of ulefnersen marking significant milestone in advancing first potential disease modifying treatment for FUS-ALS

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*– Ulefnersen demonstrated a statistically significant improvement on the primary endpoint assessing functional impairment and survival in people living with FUS-ALS, supporting the potential to modify disease progression –*

*– Results will be discussed with the U.S. FDA and health authorities globally to enable potential expedited regulatory submission pathways for approval –*

CARLSBAD, Calif.--(BUSINESS WIRE)--Sep. 22, 2026-- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) and Otsuka Pharmaceutical Development & Commercialization, Inc., today announced positive topline results from the Phase 3 FUSION trial evaluating ulefnersen, an investigational RNA-targeted medicine, in people living with amyotrophic lateral sclerosis (ALS) caused by mutations in the fused in sarcoma (FUS) gene, also known as FUS-ALS. The study met its primary endpoint, with ulefnersen demonstrating a statistically significant improvement on the primary endpoint assessing functional impairment and survival using a joint rank analysis of time to death or permanent ventilation, time to rescue[1] and change in ALS Functional Rating Scale Revised (ALSFRS-R) score from baseline to Day 505 compared to placebo (p=0.0005), providing evidence from the first-ever placebo-controlled clinical study targeting the underlying genetic cause of FUS-ALS. Ulefnersen, discovered and developed by Ionis, is the first treatment to target the underlying genetic cause of FUS-ALS and demonstrate the potential to modify disease progression.

The FUSION study also demonstrated statistically significant improvements across important secondary endpoints, including change from baseline in serum neurofilament light chain (NfL) and time to death, permanent ventilation, rescue, or withdrawal due to disease progression, further supporting the potential of ulefnersen to improve the course of disease in people living with FUS-ALS. Ulefnersen demonstrated a favorable safety and tolerability profile, with most adverse events (AE) being mild or moderate in severity.

“These groundbreaking results offer hope for the FUS-ALS community and represent an exciting milestone in our efforts to transform the treatment of this rare, rapidly progressive and fatal form of genetic ALS,” said Holly Kordasiewicz, Ph.D., executive vice president, chief development officer, Ionis. “Ulefnersen is the first investigational medicine to demonstrate a statistically significant benefit in a Phase 3 trial using a prespecified joint-rank analysis that combines assessments of function and survival, supporting ulefnersen’s potential to meaningfully modify disease progression. These unprecedented findings demonstrate the power of our science and technology for neurological diseases, and build on our experience with QALSODY, which was our first breakthrough medicine for a rare genetic form of ALS. We believe ulefnersen has the potential to be a transformative medicine for people living with FUS-ALS and are deeply grateful to the clinical trial participants and their families, investigators and advocates whose participation made this advance possible.”

Further prespecified and exploratory analyses of the data will be conducted to determine the full potential of ulefnersen for the treatment of FUS-ALS. Otsuka plans to move with urgency to review results of the FUSION trial with the U.S. Food and Drug Administration (FDA) and continue discussions with other health authorities globally regarding potential expedited submission pathways for ulefnersen approval. Ionis and Otsuka plan to present detailed results from the FUSION trial at a future medical congress and submit for publication in a peer-reviewed journal in the coming months.

“Today’s Phase 3 FUSION topline results mark a major milestone for people living with FUS-ALS, reshaping what is possible for a community that has long faced this devastating disease with limited treatment options,” said John Kraus, M.D., Ph.D., executive vice president and chief medical officer, Otsuka. “As the first FUS-ALS clinical trial to meet its primary endpoint, FUSION provides compelling evidence that a targeted genetic approach may help alter the course of disease. We are committed to working closely with health authorities to advance ulefnersen with urgency and scientific rigor and remain committed to advancing meaningful treatments for patients with significant unmet needs across neurology and rare diseases, including ALS.”

Otsuka licensed ulefnersen from Ionis in 2024 under a collaborative development and licensing agreement. Under the terms of the agreement, Ionis received an upfront payment and is eligible to receive additional regulatory and sales milestone payments as well as tiered royalties on net sales of ulefnersen.

**About the FUSION Trial**

FUSION is a global multicenter, randomized, double-blind, placebo-controlled Phase 1-3 trial evaluating the efficacy and safety of

intrathecally administered ulefnersen in people living with FUS-ALS. In Part 1 of the study, participants were randomized to receive ulefnersen or placebo during a 72-week double-blind period. Participants then entered Part 2, an open-label extension period in which all participants received ulefnersen. The primary endpoint assessed functional impairment and survival after 72 weeks using a joint rank analysis of ALS Functional Rating Scale Revised (ALSFRS-R), time to rescue, and ventilation assistance-free survival in the primary analysis population (N=73). The secondary endpoints included serum neurofilament light chain (NfL), time to death, permanent ventilation, withdrawal due to disease progression, respiratory function assessed by slow vital capacity (SVC), muscle strength assessed with handheld dynamometry (HHD), clinical function assessed by ALSFRS-R, quality of life assessed with ALS Assessment Questionnaire (ALSAQ-5), cerebrospinal fluid (CSF) NfL and CSF FUS protein.

**About FUS-ALS**

FUS-ALS is a rare form of amyotrophic lateral sclerosis (ALS) that occurs across a broad age range, including pediatric and juvenile patients, and is often rapidly progressive. It is a genetically defined subtype of ALS caused by pathogenic variants in the fused in sarcoma (FUS) gene, representing an estimated 0.6% of all ALS cases. FUS mutations are more prevalent in juvenile and pediatric ALS, accounting for an estimated 43–52% of cases. These mutations lead to the accumulation of toxic FUS protein in motor neurons, driving neurodegeneration.

In early-onset and juvenile cases, disease progression can lead to respiratory failure and death, often within 1–2 years of symptom onset. Diagnosis generally requires specialized clinical evaluation and confirmatory genetic testing. There are currently no approved therapies specifically targeting the underlying genetic cause of FUS-ALS, underscoring the critical unmet need for effective treatment options.

**About Ulefnersen**

Ulefnersen is an investigational RNA-targeted medicine designed to reduce the production of FUS protein in people with FUS-ALS, including the mutant forms that contribute to motor neuron degeneration in FUS-ALS.

By targeting the underlying genetic cause of FUS-ALS, ulefnersen represents a potential FUS-targeted therapeutic approach for people living with the disease. Ulefnersen is administered via intrathecal injection, allowing direct delivery to the central nervous system.

Ulefnersen has been granted fast track designation for FUS-ALS by the U.S. Food and Drug Administration (FDA) and orphan designation for ALS by the U.S. FDA, the European Medicines Agency (EMA) and Swissmedic.

**About Ionis Neurology**

Ionis has been at the forefront of discovering and developing leading neurological disease medicines, including ZANVASTRO™ (zilganersen), the only approved treatment for Alexander disease, SPINRAZA® (nusinersen), the first approved treatment for spinal muscular atrophy, WAINUA® (eplontersen), a medicine to treat hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN), and QALSODY® (tofersen) for SOD1-ALS. The clinical-stage portfolio includes 12 investigational medicines, of which seven are wholly owned by Ionis. Ionis' investigational portfolio includes medicines for which there are few or no disease modifying treatments, such as rare diseases including Angelman syndrome, prion disease and multiple system atrophy, as well as more common conditions like Alzheimer's disease.

**About Ionis Pharmaceuticals, Inc.**

For more than three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has marketed medicines and a leading pipeline in neurology, cardiometabolic disease and select areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients. To learn more about Ionis, visit Ionis.com and follow us on X (Twitter), LinkedIn and Instagram.

**Ionis Forward-looking Statements**

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of ulefnersen, our commercial medicines, additional medicines in development and technologies and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2025 and most recent Form 10-Q, which are on file with the Securities and Exchange Commission. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our" and "us" all refer to Ionis Pharmaceuticals and its subsidiaries.



[1] Meeting a pre-specified criterion for disease progression allowed early entry to the open-label period.

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