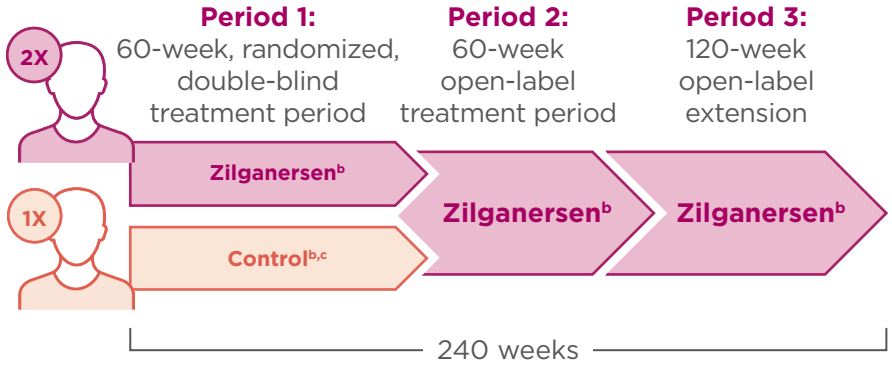
A Multicenter Study Is Evaluating Zilganersen, an Investigational RNA-Targeted Medicine, for People With Alexander Disease (AxD)

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

Study objective:
Study is to evaluate the safety and efficacy of an investigational RNA-targeted antisense medicine, zilganersen, in improving or stabilizing gross motor function across the affected domains in patients with AxD.



This is a multicenter, double-blind, controlled multiple-ascending dose, two-part study of zilganersen. **Period 1** consists of participants who will be randomized in a 2:1 ratio to receive zilganersen or control[c] for a period of 60 weeks, followed by **Period 2,** which consists of an open-label period where all participants will receive zilganersen for a period of 60 weeks. This is followed by **Period 3,** a 120-week open-label extension. Multiple dose cohorts will be evaluated in the study.

Select inclusion criteria:

- Clinical phenotype and brain imaging consistent with a diagnosis of AxD
- People aged ≥2-65 years[a,d,e]
- Documented genetic mutation in *GFAP*

For complete study information and inclusion/exclusion criteria scan here:

Table: Key Clinical Endpoints

Primary Endpoint	Change from Baseline (Day 1) through Study Week 60 in Part 1 in 10MWT[f]
Secondary Endpoints[g]	Change from Baseline in Most Bothersome Symptom Change from Baseline in GMFM-88 and PedsQL GI Scores Change from Baseline in CGIC and CGIS Scores Change from Baseline in AxD-PDIC and AxD-PDIS Scores Change from Baseline in 9-HPT Change from Baseline in In-Clinic Vineland-3 and Vineland-3 ABC Scores Change from Baseline in COMPASS-31 Score Change from Baseline in CSF GFAP Concentration

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

[a]Participants <2 years of age will be included in a separate optional, open-label, sub-study, which is only available at select sites, and which will have a different clinical trial design and endpoints than the study for individuals ≥2 years of age. [b]Administered by lumbar IT bolus injection. [c]IT placebo will continue ex-United States, and lumbar puncture control will replace IT placebo in the United States. [d]At the time of informed consent. [e]Patients <18 years old at screening must have a trial partner (parent, caregiver, or other). [f]Percent change over time from baseline to Week 61. [g]List is not comprehensive. Select endpoints in adult or pediatric populations only. Secondary endpoints are specific to part 1.

9-HPT, 9-Hole Peg Test; 10MWT, 10-Meter Walk Test; AxD-PDIC, AxD Patient Domain Impression of Change; AxD-PDIS, AxD Patient Domain Impression of Severity; CGIC, Clinical Global Impression of Change; CGIS, Clinical Global Impression of Severity; COMPASS-31, Composite Autonomic Symptom Score 31; CSF, cerebrospinal spinal fluid; GFAP, glial fibrillary acid protein; GMFM-88, Gross Motor Function Measure-88; IT, intrathecal; PedsQL GI, Pediatrics Quality of Life Inventory Gastrointestinal Symptoms Scale; Vineland-3 ABC, Vineland Adaptive Behavior Composite, Third Edition; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

1. ClinicalTrials.gov. Accessed January 18, 2024. https://clinicaltrials.gov/ct2/show/NCT04849741/ 2. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 18, 2024. https://www.ionispharma.com/ionis-technology/antisense-pipeline/ 3. Ionis Pharmaceuticals. Data on file.

Zilganersen Is an Investigational RNA-Targeted Medicine (RTM) That Has Been Designed to Reduce CNS Expression of GFAP[1-5]

Proposed Zilganersen-Mediated Downregulation of *GFAP*[1-5]

Gfap-targeting antisense oligonucleotide administration in animal models lowered levels of wild-type and mutant GFAP in the CNS, restored myelination, and reduced the concentration of Rosenthal fibers, the pathological hallmark of the disease.[4,5]

Preclinical animal models have also demonstrated improved biochemical signs and symptoms of disease.[4,5]

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For more information or questions about participating sites, please contact us at **ionisNCT048497741study@clinicaltrialmedia.com** or **844-514-7157.**[6]

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; GFAP, glial fibrillary acidic protein; mRNA, messenger RNA.

1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 2. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 18, 2024. https://www.ionispharma.com/ionis-technology/antisense-pipeline/ 3. Dhuri K, et al. *J Clin Med*. 2020;9(6):2004. 4. Hagemann TL, et al. *Ann Neurol*. 2018;83(1):27-39. 5. Hagemann TL, et al. *Sci Transl Med*. 2021;13 (620):eabg4711. 6. ClinicalTrials.gov. Accessed January 19, 2024. https://clinicaltrials.gov/ct2/show/NCT04849741/