

Alex TLC Research Summary

August 2026



Research summary of recent leukodystrophy research and clinical trials, includes article summaries and direct links to websites and articles.

Clinical trial updates

Adrenoleukodystrophy (ALD)

NEZGLYAL® (leriglitzzone) receives a positive CHMP opinion for the treatment of cerebral Adrenoleukodystrophy (cALD), a rare neurodegenerative disease

https://www.minoryx.com/media/leriglitzzone_receives_a_positive_chmp_opinion_for_the_treatment_of_cerebral_adrenoleukodystrophy/

Minoryx Therapeutics and Neuraxpharm Group have announced that European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting marketing authorisation approval under exceptional circumstances for NEZGLYAL® (leriglitzzone) as a treatment for male cALD patients, aged 2-12 years with Gadolinium (Gd) negative brain lesions. Gadolinium is a clear liquid injected for contrast to enhance MRI scans, Gd negative means the scan did not show active disease. European Commission approval is expected by the end of September 2026.

GM2 gangliosidosis

Azafaros Completes Enrollment of Phase 3 (NAVIGATE) Study Evaluating Nizubaglustat for the Treatment of Patients with GM1/GM2 Gangliosidoses

<https://www.azafaros.com/news-media/azafaros-completes-enrollment-of-phase-3-navigate-study-evaluating-nizubaglustat-for-the-treatment-of-patients-with-gm1-gm2-gangliosidoses/>

Azafaros's Phase 3 NAVIGATE study for treatment of patients with GM1/GM2 Gangliosidosis and Niemann-Pick type C disease has completed enrolment of patients with GM1/GM2 Gangliosidosis. The Phase 3 GM1/GM2 study enrolled a minimum of 75 patients across 25 clinical sites in 13 countries. The study is evaluating oral administration of nizubaglustat compared to treatment with placebo. A placebo is a treatment with no active medicine that is often used in research to compare against real treatments.

The trial is over an 18-month treatment period. Efficacy assessments will focus on neurological manifestations and disease progression. All patients treated in the study following the 18-month treatment period are eligible to continue nizubaglustat in an open label extension study, this is when after the study ends, participants are invited to join an open-label extension study. Everyone receives the new drug, this allows researchers continue to monitor safety and effectiveness over a longer period.

Research summaries

[Adrenoleukodystrophy \(ALD\)](#)

Profiling of fatty acids and lipids in animal and human tissues yields new leads for disease progression biomarkers of X-linked adrenoleukodystrophy

<https://pmc.ncbi.nlm.nih.gov/articles/PMC13234235/>

X-linked adrenoleukodystrophy (X-ALD) is a disorder caused by changes in the *ABCD1* gene. These changes disrupt adrenoleukodystrophy protein (ALDP), a protein involved in transporting very long-chain fatty acids (VLCFAs) into peroxisomes, where they are normally broken down. As a result, VLCFAs build-up throughout the body including in lipids. However, serious effects of X-ALD often occur in the central nervous system (CNS), and it remains difficult to predict how quickly the disease will progress. In this study, researchers investigated whether patterns of fatty acids and lipids could provide better biomarkers. A biomarker is a measurable biological sign, such as a blood test result, scan finding, or protein level, that helps doctors and researchers understand, diagnose, monitor, or treat a disease. They compared samples from different human tissues and body fluids, including blood and cerebrospinal fluid (CSF), as well as tissues from *ABCD1* knockout mice. The researchers found differences in lipid composition between blood and CNS tissues. This may help explain why VLCFA levels measured in blood, although useful for diagnosing X-ALD, do not reliably reflect neurological disease progression. In contrast, CSF showed lipid patterns more closely resembling those found in CNS tissues. Notably, lipidomic analysis (study of the lipids in a cell) of CSF from children with cerebral X-ALD identified several VLCFA-containing lipids that were strongly associated with disease severity, measured using the Loes score. These included ceramides, sphingomyelins, hexosylceramides and sulfatides, which are important components of myelin. The findings identify promising candidate biomarkers that could help monitor disease progression and evaluate treatment responses. Further research is needed to validate these markers and determine whether related proteins or lipid changes could eventually be detected through blood-based tests, providing less invasive ways to monitor X-ALD.

[Alexander disease \(AxD\)](#)

Neuroradiological patterns and prognostic implications in type I Alexander disease

<https://www.sciencedirect.com/science/article/pii/S1096719226004725>

Alexander disease (AxD) is a rare leukodystrophy, where Type 1 AxD usually begins in infancy or early childhood and is caused by pathogenic variants, in the GFAP gene, which provides instructions for making glial fibrillary acidic protein (GFAP) in astrocytes. Pathogenic variants are changes in the DNA that have been confirmed to cause disease. Astrocytes are the largest glial cells in the central nervous system and are involved in various cell processes including helping with communication between neurons. Children with type 1 AxD can experience developmental delay, seizures and difficulties with movement, but disease progression varies considerably. In this study, researchers investigated whether patterns seen on magnetic resonance imaging (MRI) could help predict disease progression. They analysed the first brain MRI scans from 47 people with genetically confirmed type 1 AxD from leukodystrophy centres worldwide. Patients were classified into subtypes 1a–1d, which reflect increasing levels of developmental achievement and longer-term stability. The researchers found that areas of abnormal white matter on MRI were associated with more severe disease. For example, involvement of the parietal subcortical white matter was strongly associated with type 1b AxD, a

subtype in which children do not achieve independent walking. The parietal subcortical white matter is a section of deep white matter in the midbrain between the cerebral cortex and ventricles, it controls sensory, visual, visuospatial (visual and spatial awareness), and language functions. Abnormalities in regions including the occipital and temporal white matter, corpus callosum and cerebellum, were also linked with type 1b disease. Changes in the occipital periventricular white matter helped distinguish type 1c from type 1d, potentially identifying children at greater risk of losing independent walking before adolescence. These findings suggest that MRI could provide an early prognostic tool to predict what will likely happen for type 1 AxD. The authors developed a preliminary MRI scoring system and clinical flowchart to support early disease stratification which is a system to separate people into risk groups depending on characteristics of disease. However, larger prospective studies are needed to validate these findings before the approach can be used routinely.

Fucosidosis

Longitudinal Evolution of Neuroimaging Findings in Fucosidosis: Expanding the Neuroradiologic Spectrum

<https://www.cureus.com/articles/497493#!/>

Fucosidosis is an extremely rare inherited disorder caused by the lack of an enzyme called α -L-fucosidase, which leads to the buildup of certain sugars in the brain and other organs. This case report follows an 18-year-old girl over 15 years, showing how her brain scans changed as the disease progressed. Early MRI scans at 23 months showed hyperintensity in the supratentorial compartment of the brain which is responsible for higher-level cognitive function and a hallmark of poor myelin development. Hyperintensity are areas that appear brighter due to changes in the structure or water content of the white matter due to the blood-brain barrier being affected. Subtle changes were also seen in a deep brain structure called the globus pallidus, which later became a key diagnostic clue. T1-weighted and T2-weighted MRI are different imaging sequences that change how the images appear, T1 highlights anatomical features and fat with liquids showing dark whereas T2 highlights inflammation or swelling with fluids looking bright. Over time, her scans revealed worsening involvement of the basal ganglia, including T1 and T2 signal changes and dark areas on susceptibility imaging, indicating abnormal mineral buildup. These changes eventually extended to the substantia nigra and red nuclei (structures in the basal ganglia which control movement), showing widespread metabolic injury. One distinctive feature, medial medullary lamina (layers of myelinated fibres on the thalamus) hyperintensity became more visible over the years and helped differentiate fucosidosis from other leukodystrophies. Genetic testing at age 14 confirmed pathogenic *FUCA1* mutations. The report highlights how long-term MRI follow-up can reveal the evolving pattern of white matter damage and deep grey matter mineralisation, guiding earlier diagnosis, targeted testing, and appropriate family genetic counselling.

Leigh Syndrome

Hypoxia rescues complex 1-associated disease caused by proteostatic defects

<https://www.nature.com/articles/s42255-026-01566-0>

Mitochondria are often described as the “powerhouses” of cells because they produce energy needed for cells to function. A key part of this process is the electron transport chain, which contains five protein complexes. Complex 1 is the largest and is particularly important for energy production, therefore problems affecting Complex 1 can cause mitochondrial diseases and neurological symptoms. This study investigated whether hypoxia, exposure to lower-than-normal oxygen levels, could help treat mitochondrial disease caused by defects in mitochondrial protein quality control. This study focused on HTRA2, a mitochondrial protease enzyme that helps remove damaged or misfolded proteins. In mice lacking HTRA2, proteins within mitochondria accumulated into harmful clumps. This disrupted Complex 1, reducing mitochondrial oxygen consumption and contributing to neurodegeneration and early death. The researchers found that continuous exposure to hypoxia improved HTRA2-deficient mice. Hypoxia rescued degeneration in the striatum, a brain region involved in movement, and extended lifespan. Experiments suggested that reducing oxygen levels helped restore Complex 1 protein levels and reduced signs of excessive oxygen exposure, known as tissue hyperoxia. The study also identified CLPB, a mitochondrial protein disaggregase (breaks down protein), as a partner of HTRA2. Together, HTRA2 and CLPB help maintain mitochondrial protein quality. Loss of either protein can therefore lead to protein aggregation, Complex 1 instability and disease. These findings suggest that some mitochondrial disorders caused by Complex 1 dysfunction may be responsive to hypoxia therapy. Although further research is needed before this approach can be tested clinically, the study highlights oxygen regulation as a promising therapeutic strategy for mitochondrial disease.

A phase III double-blind, placebo-controlled, randomized withdrawal trial of 5-aminolevulinic acid hydrochloride with sodium ferrous citrate for efficacy and safety in patients diagnosed as Leigh syndrome

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0332283>

This study reports the results of a phase III clinical trial testing SPP-004, a combination of 5-aminolevulinic acid (5-ALA) and sodium ferrous citrate, as a potential treatment for Leigh syndrome, a severe mitochondrial disorder that causes progressive neurological decline in children. Because no approved medication exists for Leigh syndrome, researchers evaluated whether SPP-004 could help maintain clinical improvements in patients who initially responded well to the drug. Fifty-four patients first received SPP-004 for 24 weeks. Of these, 28 showed improvement in neurological or muscle-related symptoms and entered a 48-week double-blind phase, where they were randomly assigned to continue SPP-004 or switch to placebo. A placebo is a medicine with no active medicine that is often used in research as a control to compare against the real treatment. A double-blind study is where neither the researcher nor patient know which medicine the patient is assigned. The main outcome was whether patients lost their initial improvement. The study found that the number of patients who stopped at 48 weeks due to no or lost improvement was lower in the SPP-004 group (15.4%) compared to the placebo group (50.0%). More than 80% of patients on SPP-004 maintained their clinical benefit. Safety results were encouraging; adverse drug reactions were mild and side-effect rates were similar between groups. Overall, the trial suggests that SPP-004 may help

sustain neurological improvements in Leigh syndrome and is generally safe, it represents a promising step toward developing targeted therapies for this devastating mitochondrial disease.

Please be aware these summaries are produced voluntarily by Biomedical Science students and are their interpretations of the information and findings. This information is reviewed by our Research Analyst Kristina Backlund MMSc. The National Lottery Community Fund and Ionis Pharmaceuticals, Inc have contributed to the funding of the Research Analyst role.

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