Zilganersen Trial Shows Slowed Disease Progression and Improvement in Gait Speed

Hailey was born a healthy baby, her mom says, hitting all her infant milestones like rolling over and sitting up. But at nine months old, she began falling over when she sat up and having constipation and little sleep. Her concerned mom brought it up at a pediatric appointment, but she was dismissed as being a nervous first-time parent. Four months later, the little girl had her first grand mal seizure. These seizures, along with a failure to thrive and her other initial symptoms, continued. At 16 months, she took her first steps but was always falling and was behind on her speech and other milestones. At 23 months, Hailey had a 90-minute seizure and was airlifted to a children's hospital. After an MRI and blood tests, the doctors declared her fine. It wouldn't be until Hailey was six that she finally received a diagnosis of Alexander disease, a rare neurological condition.

Previously, no drugs existed that could change the course of the disease, and treatments focused on managing symptoms. However, Ionis Pharmaceuticals' therapy, called zilganersen, recently received a breakthrough therapy designation from the Food and Drug Administration (FDA), based on encouraging clinical trial results of patients with Alexander disease.

Alexander Disease: rare, progressive, and fatal

Alexander disease is an ultra-rare, progressive neurological disorder that causes severe disability and death. The disorder is estimated to occur in around one in one to three million people worldwide. Symptoms can first appear in newborns or at any time throughout childhood and into young adulthood, with most children displaying symptoms by age four. An earlier onset typically means a more severe disease and a less likely outcome of surviving past adolescence. If the onset occurs after the age of four, symptoms may be less severe and progress more slowly. While it's rare, older adults can also be diagnosed with Alexander disease, usually with milder symptoms.

Seizures, muscle stiffness (especially an inability to control muscles for swallowing, airway protection, and purposeful movements), and developmental delays are hallmark symptoms of the disease, which can also cause an enlarged brain and/or head, hydrocephalus, feeding problems, and sleep disorders, depending on the age of onset. The disease usually leads to death within 14-25 years after symptom onset. Classified as a leukodystrophy, a group of genetic conditions that affects the brain's white matter, Alexander disease can be further categorized as a neurodegenerative leukodystrophy, meaning that over time, neurons lose their structure and functionality.

The disease is typically caused by mutations in the *GFAP* gene on chromosome 17, leading to an overproduction of an abnormal form of glial fibrillary acidic protein (GFAP). The excess GFAP then causes protein clumps to form in the arms of astrocytes, which are specialized glial cells in the central nervous system. These protein clumps, known as Rosenthal Fibers, may accumulate in the cerebral cortex, white matter of the brain, brainstem, and spinal cord, ultimately causing progressive damage to the nervous system and the symptoms of Alexander disease.

In Hailey's case, when she was five, she had learning disabilities, speech delays, was unable to walk far, and had an abnormally big head. Around this time, doctors tested her for leukodystrophy, but the results were negative. However, a young doctor became Hailey's neurologist and was determined to find a diagnosis. She was signed up for a study on children with epilepsy, which included a brain MRI, and she was also tested for Alexander disease.

A combination of clinical presentation, brain magnetic resonance imaging (MRI) findings, and genetic testing is used to diagnose the disease. Interventions, including physiotherapy, speech therapy, nutrition, and anti-epileptic drugs, can help manage symptoms as the disease progresses. But before zilganersen — an antisense oligonucleotide therapy that blocks the excess production of GFAP caused by a mutation in the *GFAP* gene — no treatments existed that actually aimed to stop the accumulation of the damaging protein.

The global trial and results: statistically significant and clinically meaningful

The breakthrough therapy designation was granted based on results from a phase 1-3 multiple ascending dose study that assessed the safety and efficacy of zilganersen in 54 participants aged 1.5 to 53 years with genetically confirmed Alexander disease. The participants, most of whom were children, were randomly assigned 2:1 to receive either 25mg or 50mg of zilganersen or placebo via intrathecal bolus (ITB) once every 12 weeks for a 60-week double-blind treatment period. After the 60-week double-blind period, participants transitioned into open-label treatment, followed by a 120-week long-term extension phase, in which those receiving the 25 mg dose began receiving 50 mg.

Results of the global trial, which took place across 13 sites in eight countries, showed that those receiving the 50mg dose of zilganersen had a statistically significant and clinically meaningful improvement from baseline in gait speed compared to placebo at week 61, as assessed by the 10-meter walk test, which found a mean improvement of 33% in patients given the higher dose. The results also demonstrated consistent favorable trends across key secondary endpoints, including patient- and clinician-reported measures that indicate slowed disease progression, stabilization, or improvement. The therapy was safe and well-tolerated, with most adverse events being mild or moderate. Serious adverse events occurred less often in the zilganersen group than in the placebo group.

“People living with Alexander disease have gone far too long without a treatment capable of changing the course of their disease, which makes this Breakthrough Therapy designation particularly meaningful,” said Holly Kordasiewicz, PhD, Executive Vice President, Chief Development Officer at Ionis, in a press statement. “Our pivotal zilganersen study provides the first evidence that an investigational treatment can modify the underlying disease and improve outcomes, representing an important step forward for the Alexander disease community.”

An open-label sub-study for patients under age two continues, and enrolled participants can access zilganersen in the long-term extension.

Previous trial and FDA designations

In 2020, zilganersen was granted Orphan Drug designation and Rare Pediatric designation by the U.S. Food and Drug Administration (FDA). Additionally, in 2019, the European Medicines Agency (EMA) granted zilganersen an Orphan Drug designation.

In 2021, Ionis Pharmaceuticals successfully treated rats exhibiting features of Alexander disease with zilganersen. The study found that rats treated at three weeks old, before the onset of noticeable symptoms, were physically indistinguishable from normal rats. The group that was treated at eight weeks old, when severe impairment was present, had the Rosenthal fibres disappear within a few weeks after one injection, and several disease markers returned to levels close to normal (1). The encouraging results of this study enabled Ionis to continue on to the recent clinical trial.

Future of zilganersen and those with Alexander disease

After Hailey received the diagnosis, she continued to attend school with the help of an aide. Recently, the now 20-year-old graduated from high school.

“Hailey loves to draw in her sketchbook, enjoys watching cooking shows, and wants to be a chef when she grows up,” her mom says. “She has quite a collection of Barbie dolls, loves the color pink, shopping, and trying new restaurants.”

Despite this, the young woman still has significant learning disabilities, struggles to walk, and has a speech that is difficult to understand, her mom says.

“A treatment could mean Hailey could stay stable, or perhaps it might get her walking better and not need her wheelchair,” her mom says. “I believe it will happen and increase her quality of life.”

The breakthrough therapy designation is a positive step forward for patients like Hailey and their families, with zilganersen providing a potential treatment for not just managing symptoms, but changing the course of their disease. According to the company, Ionis plans to file a new drug application in the early months of 2026 and is working to initiate an expanded patient access program in the U.S.

1. Hagemann TL, Powers B, Lin NH, Mohamed AF, Dague KL, Hannah SC, Bachmann G, Mazur C, Rigo F, Olsen AL, Feany MB, Perng MD, Berman RF, Messing A. Antisense therapy in a rat model of Alexander disease reverses GFAP pathology, white matter deficits, and motor impairment. Sci Transl Med. 2021 Nov 17;13(620):eabg4711. doi: 10.1126/scitranslmed.abg4711. Epub 2021 Nov 17. PMID: 34788075; PMCID: PMC8730534.