Plain Language Summary

Neuroprotective effect of N-acetyl-L-leucine in adult and pediatric patients with Niemann-Pick disease type C

Citation: Patterson MC, Ramaswami U, Donald A, Foltan T, Gautschi M, Gissen P, Hahn A, Jones SA, Kay R, Kolniková M, Park J, Reichmannová S, Walterfang M, Wibawa P, Rohrbach M, Martakis K, Bremova-Ertl T. Disease-Modifying, Neuroprotective Effect of N-Acetyl-l-Leucine in Adult and Pediatric Patients With Niemann-Pick Disease Type C**.** Neurology. 2025 Jul;105(1):e213589. Study on N-Acetyl-L-Leucine (NALL) for Niemann-Pick Disease Type C (NPC)

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Plain Language Summary: Results of a long-term extension of a Phase III trial on the safety and efficacy of N-acetyl-L-leucine in adult and pediatric patients with NPC

Niemann-Pick disease type C (NPC) is a rare and serious progressive genetic disease, meaning it gets worse over time. It causes a wide range of problems, especially with the brain and nervous system like issues with movement (also known as ataxia), balance, speech, and thinking, which significantly impact a person's daily life.

About the Study:

- **What they wanted to find out:** This study, an extension of a previous phase 3 trial, aimed to evaluate the long-term safety and effectiveness of N-acetyl-L-leucine (NALL) in patients with NPC.
- **Who participated:** 53 patients with a confirmed genetic diagnosis of NPC, ranging in age from 5 to 67 years old, were enrolled in this extension phase. These patients had all completed an earlier placebo-controlled trial.
- **How it was done:** This was an "open-label" study, meaning all participants and researchers knew the patients were receiving NALL. Patients took NALL orally 2–3 times per day, with dosing adjusted for weight. The study followed patients for 12 and 18 months.
    - To measure changes, researchers used the modified 5-domain NPC Clinical Severity Scale (NPC-CSS), which assesses areas like ambulation, cognition, fine motor skills, speech, and swallow. A lower score indicates better neurological status.
    - The results from patients on NALL were compared to the expected rate of disease progression observed in historical studies of NPC patients who did not receive NALL.
- **What they measured:** The primary goal was to assess changes on the 5-domain NPC-CSS. They also used other scales, including the 15-domain and 4-domain NPC-CSSs, and the Scale for Assessment and Rating of Ataxia (SARA), to evaluate balance, coordination, and overall neurological status. Safety was continuously monitored through adverse event reporting, lab tests, and physical examinations.

What the Study Found:

- **Slowing Disease Progression:**
    - After 12 months, patients receiving NALL showed a mean change of -0.27 points on the 5-domain NPC-CSS, while historical cohorts typically showed an increase of +1.5 points. This indicated a significant reduction in annual disease progression, effectively improving the patients' condition compared to the expected decline.
    - These positive effects were sustained at 18 months, with NALL-treated patients showing a mean change of +0.05 points compared to an expected +2.25 points in historical cohorts.

- Improvements in neurological manifestations, as measured by the SARA, were also sustained over the long-term follow-up, reinforcing NALL's beneficial impact on symptoms.
- The benefits of NALL were consistent across both pediatric and adult patients, and whether or not they were also taking another NPC medication called miglustat.

- **Safety:**
  - NALL was found to be well tolerated throughout the study.
  - No treatment-related adverse events or serious reactions occurred, and no patients discontinued the study due to side effects.

What This Means:

This study provides strong evidence that NALL can significantly reduce the progression of NPC over 12 and 18 months, demonstrating a disease-modifying effect. The sustained improvements in neurological symptoms and the favorable safety profile are important findings.

While this extension phase was open-label (meaning participants and researchers knew NALL was being administered), the comparison to well-established historical disease progression rates provides insight into NALL's benefit over an extended time period. These results suggest that NALL can offer both rapid symptom improvement and longer-term disease modification.