# LAY SUMMARY OF STUDY RESULTS

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| **Study Title:** | A Prospective, Longitudinal Study of Potential Treatment-Responsive Biomarkers and Clinical Outcomes in Hunter Syndrome |
| **Study Number:** | DNLI-E-0001 |
| **Name of Investigational Product:** | Not applicable |
| **Indication Studied:** | Hunter syndrome (Mucopolysaccharidosis type II) |
| **Development Phase of the Study:** | Not applicable |
| **Study Sponsor:** | Denali Therapeutics Inc.<br>161 Oyster Point Blvd<br>South San Francisco, CA 94080<br>USA |
| **Study Dates:** | First Participant Signed Informed Consent Form: 23 October 2019<br>Last Participant, Last Visit: 01 March 2024 |
| **Report Type:** | Final Report |
| **CSR Final Date:** | 28 April 2025 |

## Rationale

This study observed how mucopolysaccharidosis type II (MPS II) changes over time and looked for biomarkers that might respond to treatment. It included the neuronopathic form of MPS II (nMPS II), which affects the brain. The goal was to better understand these biomarkers and how they relate to signs and symptoms of MPS II as the disease gets worse over time.

The purpose of the study was to look at biomarkers that might be linked to how severe the disease is or how it responds to treatment. The study also followed how the disease changed over time in people with MPS II. No study drug was given. Some participants were receiving standard enzyme-replacement therapy (ERT), and some were not. This therapy was given intravenously, meaning it was put directly into a vein.

Doctors measured several health outcomes during the study. These included tests of thinking and behavior, lab tests, and checks of certain substances in the body called biomarkers. Biomarkers in blood, spinal fluid (also called cerebrospinal fluid or CSF), and urine were tested to better understand how the disease affects the body. The researchers also looked at how these biomarkers related to how severe the disease was, based on medical exams and thinking tests.

## Objectives of the Study

The main goals of the study were:

- To track changes in daily life skills using a test called the Vineland Adaptive Behavior Scales™ (VABS)

- To track changes in thinking and learning using one of the following tests, depending on the child's age:
    - Bayley Scales of Infant and Toddler Development™, Third Edition (BSID-III)
    - Kaufman Assessment Battery for Children™, Second Edition (KABC-II)
    - Wechsler Intelligence Scale for Children®, Fifth Edition (WISC®-V)
- To measure levels of certain biomarkers in blood, urine, and/or spinal fluid (CSF) that may be linked to the disease or may change with treatment in people with MPS II

**Methodology**

This was a six-part, prospective, multicenter, multiregional, observational study designed to evaluate biomarkers and assess the clinical outcomes of disease in patients with MPS II, including nMPS II and nnMPS II. Eligible participants were required to have a documented diagnosis of MPS II, which included genetic analysis (ie, mutation analysis of the iduronate 2-sulfatase [*IDS*] gene) and biochemical assessment (eg, IDS enzyme activity in plasma, white blood cells, or fibroblasts). No experimental therapies were administered in this study.

This was a six-part, forward-looking study that took place at several centers in different regions. It was an observational study, meaning no new treatments were tested. The goal was to study biomarkers and track how the disease affects people with MPS II, including both types: neuronopathic (nMPS II) and non-neuronopathic (nnMPS II).

To join the study, participants had to have a confirmed diagnosis of MPS II. This included a genetic test showing a change (mutation) in the iduronate 2-sulfatase (IDS) gene and lab tests showing IDS enzyme activity in the blood, white blood cells, or skin cells (called fibroblasts). No experimental treatments were given during the study.

Planned total enrollment in the study was approximately 39 participants with MPS II; actual enrollment was 18 participants. No nnMPS II participants were enrolled.

**Participant Disposition**

A total of 20 participants were screened for study eligibility, and 18 participants were enrolled in and completed the study per the protocol definition. Two of the 20 participants in the Screened Population screening failed; however, upon further subsequent testing, both participants met the eligibility criteria for and enrolled directly in the interventional Phase 1/2 open-label study with DNL310 (Study DNLI-E-0002).

Overall, most participants (10 of 18) were enrolled in Part 1 of the study. Two participants were enrolled in and completed Part 2, none were enrolled in Part 5, and the remaining participants were enrolled in Part 3 (n = 2), Part 4 (n = 1), and Part 6 (n = 3). No Part 1 participants switched into Part 3 or Part 4.

**Participant Demographic and Other Baseline Characteristics**

All 18 (100%) participants were male. Most of the participants were White (12 [66.7%]). The average age when they joined the study was 63.4 months. A total of 6 of 18 (33.3%) participants were aged < 4 years at the time of informed consent, and 12 of 18 (66.7%) were aged ≥ 4 years at the time of informed consent.

The most common gene change found in the study was a missense variant, seen in 9 out of 18 participants (50.0%). The other half of the participants (50.0%) had different types of more serious gene changes. These included large deletions, rearrangements, stop-gained changes, nonsense variants, frameshift variants, or splice variants. Among these, the frameshift variant was the most common, found in 3 participants.

For all 18 participants in the study, the average age when they were diagnosed with MPS II was 27.4 months (about 2 years and 3 months) and the average time they had been living with the disease was 3.0 years. Most of the participants (16 out of 18, or 88.9%) had a developmental quotient below 85 when they were first screened for the study.

Overall, 16 of 18 participants had a prior or ongoing history of ERT use.

**Conclusions**

- Adaptive behavior and thinking skills stayed the same or got worse over time.
- Standard test scores went down compared to other children the same age.
- Spinal fluid biomarkers were high and varied by age.
- Urine biomarkers were high.
- Blood biomarkers showed small and mixed changes.
- Serum NfL was elevated and correlated moderately with adaptive behavior raw scores.