

September 2026

Denali Therapeutics Update for the MPS IIIA Community: Information About the DNL126 Research Program

MPS IIIA Families and Community,

We are pleased to share an update on our work to advance a potential treatment for Sanfilippo syndrome type A (MPS IIIA). This update provides an overview of the ongoing Phase 1/2 study of DNL126, including what the study is designed to evaluate, future plans for a global Phase 3 confirmatory study, and answers to questions we have heard from families, advocates, and community organizations.

DNL126, also known as zafinofusp alfa, is an investigational enzyme replacement treatment (ERT), which means its safety and effectiveness have not been established and it has not been approved by any health authority.

We are grateful to the children and families participating in the study, as well as the study physicians and study teams supporting this research. Their time and commitment are informing the continued development of DNL126 and advancing the broader scientific understanding of MPS IIIA.

The Phase 1/2 study is ongoing, so this update does not include new study results or individual participants' experiences. Initial Phase 1/2 study results were presented at *WORLDSymposium™ 2026*, a scientific conference focused on lysosomal storage diseases, and have also been shared at recent family and community conferences. Early findings from the Phase 1/2 study are encouraging and have led to plans for a global Phase 3 confirmatory study. Longer-term study results will be shared at a scientific conference in early 2027.

We understand that the community has important questions about DNL126. The frequently asked questions below address what we can share today, while recognizing the study is ongoing and that we will continue to learn.

Frequently Asked Questions

What questions is the Phase 1/2 study designed to answer?

The study is designed to help researchers:

- Understand the safety and tolerability of DNL126.
- Determine the optimal dose of DNL126 and how frequently it should be given by infusion.
- Determine the impact of DNL126 on disease-related biomarkers at different timepoints, as well as early information on clinical outcomes.
- Use these learnings to inform plans for the future global Phase 3 confirmatory study.

What biomarkers and clinical outcomes are researchers measuring in the Phase 1/2 study?

Biomarkers are biological signs that help researchers understand what is happening in the body and whether a treatment may be affecting the disease. The biomarkers measured in this study include:

- **Heparan sulfate (HS):** a substance that builds up in the body and brain in MPS IIIA
- **GM3:** a marker of dysfunction within lysosomes, the parts of cells responsible for breaking down and recycling certain substances
- **Neurofilament light chain (NfL):** a marker associated with injury to nerve cells, including those in the brain

Clinical outcomes help researchers understand how participants feel, function, and develop. Clinical outcomes being assessed in this study include neurocognitive development and behavior, sleep, hearing, liver volume, and bowel movements.

Together, these biomarkers and clinical measures help researchers build a broader understanding of the effects of DNL126 over time.

Why did Denali design the Phase 1/2 study to include children of different ages and at different stages of disease?

We recognize that MPS IIIA affects children across different ages and stages of disease. Through our conversations with families and advocates, we have also heard how important it is for research to reflect this range of experiences. Including participants across a range of ages and disease stages may help researchers understand the experience with DNL126 across a broader group.

What is known about infusion-related reactions with enzyme replacement therapies?

Infusion-related reactions are a recognized side effect with enzyme replacement therapies used to treat lysosomal storage diseases. The type, frequency, and severity of these reactions can vary by treatment and by individual.

Depending on the treatment and a patient's individual needs, physicians may use several approaches to help manage infusion-related reactions. These may include giving medications before or after an infusion, gradually increasing the dose, adjusting the infusion rate, and monitoring the participant closely during and after treatment.

In clinical studies, including the DNL126 Phase 1/2 study, decisions to help manage reactions are made by the study physician, within the guidance of the study protocol and tailored to individual participants. The goal is to make the treatment experience as safe and comfortable as possible. The DNL126 study physicians and Denali collaborate and share emerging learnings to inform how infusion-related reactions are managed and how participants can best be supported.

While experience with other enzyme replacement therapies provides important context, every therapy is different. The safety and tolerability of DNL126 must continue to be evaluated through the ongoing study.

What is immune tolerance induction, or ITI?

The immune system may recognize an enzyme replacement therapy as foreign, particularly when the body makes little or none of the working enzyme naturally, as in MPS IIIA. This can lead to the production of proteins called anti-drug antibodies, or ADAs. This type of immune response has been observed with many enzyme replacement therapies used to treat lysosomal storage diseases and other diseases. High levels of ADAs may interfere with how an enzyme replacement therapy functions in the body.

Immune tolerance induction, or ITI, uses a combination of medicines intended to reduce or manage this immune response.

How has the approach to ITI evolved across the DNL126 Phase 1/2 study and future Phase 3 study?

Early studies of new treatments often provide important information that was not known when the study began. As the Phase 1/2 study has progressed, Denali and the study physicians continue to review information and learn from participants' experiences.

Based on this ongoing review, the study protocol was updated to allow immune tolerance induction (ITI) as an option for certain participants who have developed, or may be at risk of developing, high levels of anti-drug antibodies. In alignment with the study protocol, the study physician will work with each family to determine whether ITI is appropriate for the individual participant. The impact of using ITI at different points in treatment will continue to be studied.

Building on these learnings, Denali plans to include ITI medications in the future global Phase 3 study of DNL126.

Why is long-term study participation and follow-up important?

Long-term participation and follow-up in a clinical study help researchers develop a more complete understanding of an investigational therapy, including its safety, tolerability, and its effects on biomarkers and clinical outcomes over time.

Denali plans to seek accelerated approval of DNL126 from the U.S. Food and Drug Administration (FDA) using cerebrospinal fluid heparan sulfate, or CSF HS, as a biomarker that may predict clinical benefit. Because accelerated approval may be based on a biomarker before clinical benefit is fully understood, collecting longer-term data is especially important. Continued follow-up in the Phase 1/2 study, together with the future global Phase 3 study, will help researchers understand whether biomarker changes are associated with meaningful clinical benefit over time.

We recognize that study participation is demanding, and each family must decide what is right for their child and family. Families may choose to stop participating in a clinical study for many reasons, and we are grateful for every family's contribution.

What are the next steps for the DNL126 clinical program?

Early results from the Phase 1/2 study are encouraging. These initial findings have led to plans for a global Phase 3 confirmatory study and a future regulatory submission to the FDA seeking potential accelerated approval.

As the Phase 1/2 study continues and plans for the Phase 3 study are finalized, we will continue to keep the community informed through community letters and in collaboration with patient advocacy organizations.

We recognize the urgency felt across the MPS IIIA community. As we continue this work, we remain focused on learning responsibly, listening closely, and keeping the experience of study participants at the center of our decisions. Families with questions about their participation in the study are encouraged to speak openly with their study physician and study team, who are there to listen, answer questions, and support families.

The MPS IIIA community may contact the Denali Patient Advocacy team with questions at patientadvocacy@dnli.com.

With gratitude,

The Denali Team
Denali Therapeutics

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