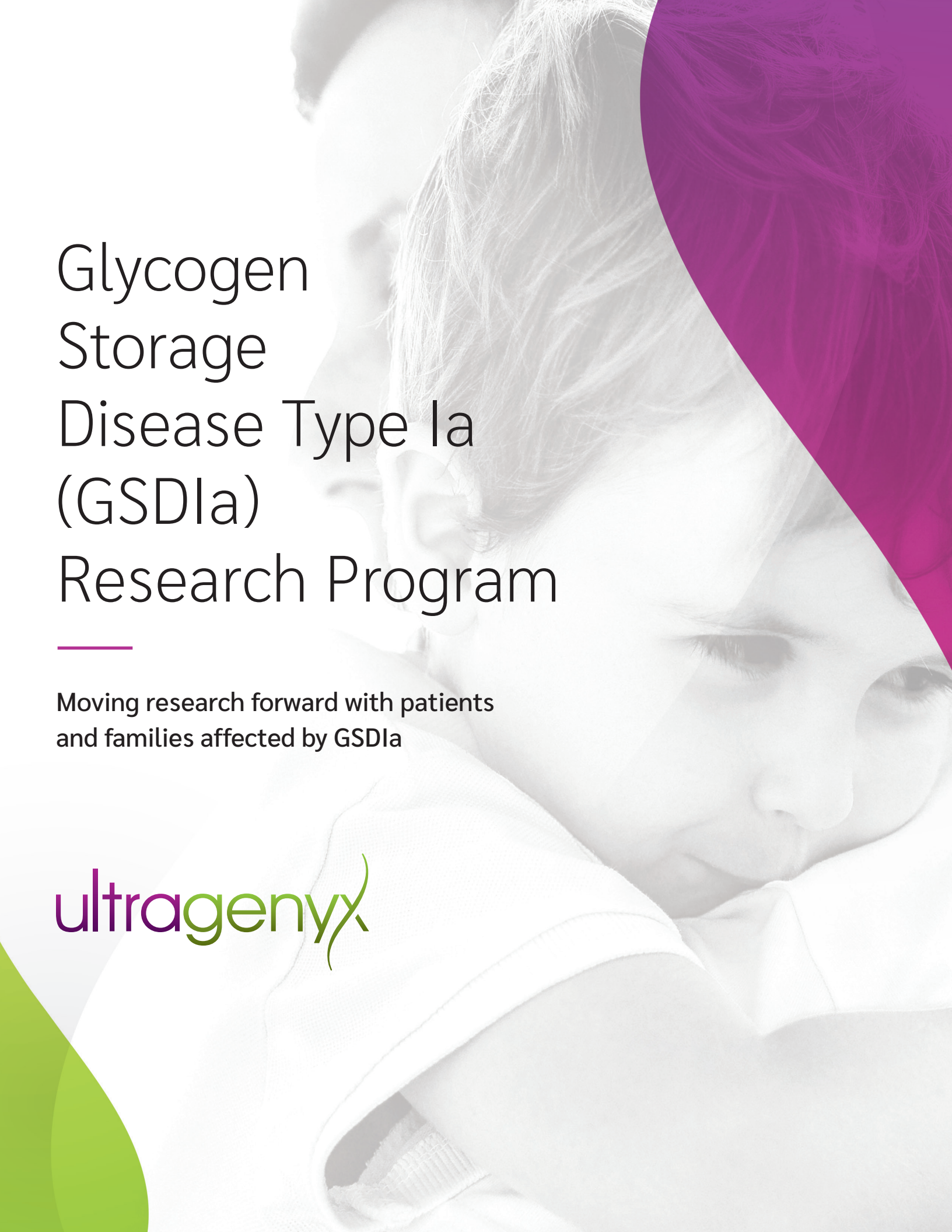

# Glycogen Storage Disease Type Ia (GSDIa) Research Program

Moving research forward with patients and families affected by GSDIa

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## Commitment

Ultragenyx has a long-standing commitment to developing treatments for rare and ultrarare diseases—providing treatments where none previously existed. We view you and your community as our partners working toward the same goal of finding a safe and effective treatment for GSDIa. That's why we have a responsibility to give you a clear view of our gene therapy research programs.

## Community

We recognize that people living with rare diseases and their families are the experts on their conditions. That's why we engage the GSDIa community, in addition to health care providers, as partners in advancing research. Your experiences drive this research forward.

# A Need to Revolutionize Treatment for GSDIa

## Living with GSDIa

The impact of GSDIa on patients' and caregivers' daily lives has not been studied very much in the past.[1] In addition to the physical symptoms, GSDIa can cause mental and emotional burdens that are impossible for people not affected by GSDIa to understand.[2] At Ultragenyx, we want to change that. So, we listened and learned what it's like from people living with GSDIa and their family members. The insights we gained helped us better understand the impact of this disease—and how we can help.

People living with GSDIa need continuous glucose supplementation and dietary management—all day and all night. This means sticking to a strict eating and drinking schedule, including frequent cornstarch consumption.[1] Missing even a single dose of cornstarch increases the risk of hypoglycemia, which can lead to severe complications and even death.[3]

During our research, we gathered stories from the GSDIa community. We learned that patients and caregivers feel a need for "constant vigilance" to manage their health. This includes the need to wake up during the night to consume cornstarch, leading to poor sleep and impacting school, career and social life—effects felt by the entire family.[2]

## Time for a Potential New Therapy

Right now, strict dietary management and regular doses of uncooked cornstarch are used to manage the symptoms of people with GSDIa. However, cornstarch and diet do not correct the underlying cause of disease, and the risk of serious long-term complications still remains.[1,3] Frequent cornstarch consumption in large volumes can be burdensome and may be associated with an increased risk of metabolic syndrome.[3]

This is why new treatment options are being studied. It is hoped that these new treatments will address the underlying cause of the disease itself in a way that current options do not.[4]

At Ultragenyx, we are studying a gene therapy designed for people living with GSDIa. Using gene therapy, our goal is to look deeper and target the underlying cause of disease, compared with standard therapies that treat the symptoms.

> "Simple things such as getting a good night sleep are impossible for me, as I have to wake up every four hours in order to consume cornstarch...so I am constantly exhausted and deprived of sleep."
>
> — *Person living with GSDIa describing their experiences during an Ultragenyx observational study*[2]

# The Gene Therapy Development Process

This is an overview of the gene therapy research and development process. To learn more, visit the American Society of Gene & Cell Therapy (ASGCT) website. Different types of studies in animals (nonclinical) and humans (clinical) help to explain how a potential treatment will interact with the human body and impact a patient's disease. Each type of research helps us better understand the potential treatment.[5]

## PRECLINICAL RESEARCH

Test the treatment in animal models to determine if it is safe to test in humans.[5] The beginning stages of rare disease drug development often rely on scientists, clinicians, patients and families who collaboratively drive research to identify potential new therapies.[6] The work of people living with GSDIa, their families, advocacy groups and researchers during this stage is sincerely appreciated by Ultragenyx.

## INVESTIGATIONAL NEW DRUG (IND) APPLICATION IN THE UNITED STATES (U.S.)

Submit the preclinical study data and clinical development plan in an IND application to the U.S. Food and Drug Administration (FDA). The FDA will review the IND application to determine if the treatment should move to a clinical trial.[5] Other countries require similar application and review processes before any potential treatment can be studied in people.[7]

## PHASE 1/2 CLINICAL TRIALS

Test if the therapy is safe for a small number of participants in a Phase 1 study. Then test in more participants with the disease in Phase 2 to ensure the treatment is safe in individuals with the disease and determine the proper dose. These phases are often combined for gene therapy clinical trials, especially in people with rare diseases.[5]

Ultragenyx completed a Phase 1/2 study of a one-time intravenous (IV) infusion of DTX401*, an investigational gene therapy for GSDIa. These results were presented at several medical conferences, including the International Congress of Inborn Errors of Metabolism, American Society of Gene & Cell Therapy, European Society of Gene and Cell Therapy, and International Glycogen Storage Disease Conference.[8-10]

**About this study[10]:**

- A global, multicenter, open-label, Phase 1/2 study evaluated the safety and preliminary efficacy of a single IV infusion of DTX401 in adults with GSDIa
- The study's main purpose was to evaluate the safety of DTX401 and determine the optimal dose to use in a larger randomized, controlled, Phase 3 study
- A total of 12 adults with GSDIa were treated with DTX401 and followed for 52 weeks after dosing. After completion of the 52-week portion of the study:
  - All participants opted to enroll in a four-year extension study to evaluate the long-term (a total of five years) safety and efficacy of DTX401
  - Ultragenyx conducted interviews with participants to help our team define the outcomes that are most meaningful to people with GSDIa and their families. This type of research allowed them to describe their experiences in their own words, which goes beyond the information that can be captured in a survey or other trial assessment

## OBSERVATIONAL RESEARCH

Observational research plays an important role in drug development, and it often happens at the same time clinical trials are being done. It helps us build on what we know about living with GSDIa and understand the challenges and needs of patients and families affected by GSDIa. We conducted three different health economics and outcomes research (HEOR) studies to learn more about people living with GSDIa.[11]

### *Understand the health care system experience of people living with GSDIa*

**About this study[13]:**

- Hospital episode statistics data from the National Health Service (NHS) hospitals in the United Kingdom (U.K.) from April 2015 through December 2020 were analyzed
- The goals were to understand whether people living with GSDIa require more medical care than people without GSDIa and the hospital experiences for people living with GSDIa
- An analysis of medical records from 934 people living with GSDIa identified that:
  - People living with GSDIa had more medical complications compared with the overall population. The most common complications were low red blood cell count, digestive issues and low blood sugar
  - People living with GSDIa had more than four times the number of hospitalization events and two times the number of outpatient visits per year compared with the average patient

### *What is HEOR?*

HEOR aims to understand the benefits of a treatment beyond the efficacy of the therapy itself. These studies can help identify gaps in care and areas for quality-of-life improvement, understand the burdens of disease or existing treatment on the lives of patients and explore the potential impact of new therapies on patients and health care systems. HEOR data may be used to help educate regulatory agencies or insurance companies on the needs of patient communities throughout the development process.[12]

### *Learn about the GSDIa community's challenges, worries and concerns through personal stories*

**About this study[2]:**

- Researchers asked people living with GSDIa and their caregivers from the U.S. and U.K. to write firsthand accounts of their experiences with GSDIa. Participants could write as much as they wanted, about anything they wanted
- The goal was to understand what parts of the daily lives of patients and caregivers are impacted most by GSDIa
- A total of 11 patient and eight caregiver accounts were collected, revealing key challenges:
  - GSDIa has a substantial impact on the lives of patients and caregivers
  - Burden of managing cornstarch and diet
  - Issues with diagnosis and the health care system
  - Impacts on mental health, social relationships, daily activities, work and family life
- Many of the participants expressed a desire for new treatment

### *Measure the impact of GSDIa on health-related quality of life*

**This study had two parts:**

**Part 1:** Three sources of information were combined to create hypothetical situations of patients with GSDIa, their caregivers and their quality of life[1]:

- A review of published literature that identified key areas of disease burden
- Interviews with expert GSDIa clinicians
- Interviews with caregivers of people living with GSDIa

The hypothetical situations included patients of different ages with varying clinical experiences with GSDIa and different levels of response to a potential new treatment.[1]

**Part 2:** After the hypothetical situations were created, they were shown to 100 random people from the general U.K. population who were asked to imagine themselves in the situations as a patient with GSDIa or caregiver, and then they answered health-related quality-of-life questions. The goals of these interviews were to understand the quality of life of people affected by GSDIa and the impact of a potential new treatment.[1] Conducting this type of research among a general population of unaffected individuals can help health care decision-makers understand the severity of a condition and the need for new treatments.

**From these interviews, we learned that[1]:**

- Daily living of both patients and caregivers affected by GSDIa is negatively impacted due to frequent cornstarch consumption and a strict diet
- A treatment that may reduce the need for cornstarch and a strict diet would help to make the quality of life better for both patients and caregivers affected by GSDIa

The impacts of GSDIa on daily life identified in this study are consistent with findings from a survey including 27 adult patients with GSDIa from Germany.[14]

## PHASE 3 CLINICAL TRIALS

Test if the treatment gives the desired result while remaining safe in an even larger group of participants. This phase is the longest and includes the greatest number of participants.[5]

*GlucoGene: Studying Gene Therapy for GSDIa*

**About GlucoGene[4]:**

- A Phase 3 study designed to determine the safety and efficacy of a one-time IV infusion of gene therapy, DTX401*, when compared with placebo
- Approximately 50 people living with GSDIa (ages eight years and older) who currently receive cornstarch regularly as part of their dietary regimen are enrolled in this study. People were recruited from the U.S., Canada, Europe and Latin America
- The goals of this study are to evaluate if DTX401 can help people with GSDIa maintain or improve blood sugar levels with less or no cornstarch. This study will also continue to evaluate the safety of DTX401 and determine if DTX401 can improve quality of life
- What's involved:
  - Patients receive a single IV infusion of either DTX401 or placebo
  - Patients who receive placebo will receive DTX401 after 48 weeks, if still eligible
  - All patients have been asked to maintain confidentiality of their participation and avoid sharing their experience on social and regular media, including whether or not the individual believes they received placebo or DTX401

*Enrollment for the Phase 3 study is complete, and the study is currently ongoing. We will share results once the study has been completed.*

## LONG-TERM FOLLOW-UP

After Phase 1/2 or Phase 3 clinical trials, follow-up studies that extend beyond the initial trial are required to monitor long-term safety and efficacy of gene therapy products. Information collected from a study participant's ongoing experiences is critical to fully understand the benefits and risks of gene therapy. Without this information, it may not be possible to advance research as quickly.[4]

*DTX401 is an investigational adeno-associated virus (AAV) gene therapy designed to deliver a functional *G6PC* gene.[4] Additional studies are required to make definitive conclusions about the safety or efficacy of this potential treatment. DTX401 is not approved by the FDA or any other regulatory agencies.

## FDA FINAL APPROVAL†

If data from a Phase 3 study show the treatment is safe and effective, a Biologics License Application (BLA) can be submitted to the FDA. Treatment can only become available in the U.S. if the FDA accepts the BLA and approves the treatment for use in GSDIa.[5]

The goal of Ultragenyx is to develop a new therapy with the potential to treat as many people living with GSDIa as possible. Conducting clinical trials in multiple countries may allow companies like Ultragenyx to submit applications to other global regulatory agencies for a product approval.

The FDA and other regulatory agencies, including from the European Union (EMA), U.K. (MHRA), Japan (PMDA), Canada (Health Canada) and Brazil (ANVISA), may look to each other to determine whether or not to approve the treatment for use in their country or region.[15]

## PHASE 4 CLINICAL TRIALS

After the FDA or other agencies approve a new treatment, its long-term effects may be studied in a Phase 4 postmarketing study. Phase 4 monitoring of a new treatment allows the reporting of long-term benefits or additional risks not seen in the shorter observation period during earlier phases of research.[16]

This will be especially important for gene therapy because it is currently being studied as a one-time treatment.[5] Longer-term studies, such as a Phase 4 study, may help to understand the durability of gene therapy products. (Durability is the length of time that a patient will continue to experience a therapeutic effect from the treatment.)

†It is not guaranteed that DTX401 will make it to FDA approval. This step only occurs if research shows the treatment is safe and effective.

# Our Partnership With the GSDIa Community

Our goal is to create gene therapies with the potential to change lives by learning from those directly impacted. You bring something that science, alone, never can—personal experience living with the condition.

**Some ways we are continuing to learn from you and your community include:**

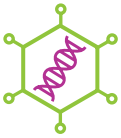
- In-person or virtual small-group meetings, called advisory boards
- Ongoing engagement with the community through patient advocacy organizations
- Interviews with community members

## A Collaborative Effort

Ultragenyx is grateful to all patients, caregivers and families who have contributed to GSDIa research. Research progress would not be possible without you.

## You Can Help Move GSDIa Research Forward

Patient communities and organizations can get involved in rare disease therapy development and help advance research. Sharing your experience living with GSDIa can help raise awareness and demonstrate the need for, and impact of, new therapies.



## Learn More About Gene Therapy

Visit the American Society of Gene & Cell Therapy's patient education website at **www.patienteducation.asgct.org** to learn more about gene therapy and the gene therapy development process.

## Connect With the Patient Advocacy Team at Ultragenyx

Visit **www.UltraRareAdvocacy.com** or email **PatientAdvocacy@Ultragenyx.com** to stay in touch with the Patient Advocacy team and access further information about GSDIa and gene therapy.

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