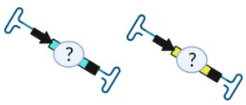
Gene Therapy Clinical Trial for Tay-Sachs and Sandhoff Diseases

At Sio, we operate with a sense of urgency and compassion to develop gene therapies that transform the treatment of serious neurodegenerative diseases. We combine cutting-edge science with rigorous testing to fill unmet medical needs for patients with therapies that are intended to deliver lifelong benefits.

Tay-Sachs & Sandhoff Diseases (GM2 Gangliosidosis)



GM2 is a fatal disease caused by a mutation in either the *HEXA* (for Tay-Sachs disease) or *HEXB* (for Sandhoff disease) genes. Without working copies of these genes, HexA enzyme levels are low and lead to accumulation of toxic storage materials in neurons in the brain and spinal cord. No disease modifying treatments are currently available.

AXO-AAV-GM2 Gene Therapy Clinical Study for GM2 Gangliosidosis

A Phase 1/2 clinical trial is being conducted to learn if an experimental gene therapy called AXO-AAV-GM2 can help treat children with infantile and juvenile-onset GM2 gangliosidosis. AXO-AAV-GM2 delivers working copies of the HEXA and HEXB genes. This trial consists of two stages as shown below. Detailed information about the trial and eligibility requirements are listed at www.clinicaltrials.gov (Identifier: NCT04669535).

STAGE 1: Dose Ranging

Goal is to assess safety & identify the optimal dose

- High-Dose (~ 4 patients)
- Mid-Dose (~ 4 patients)
- Low-Dose (2 patients)
- Starting Dose (1 patient)

STAGE 2: Efficacy & Safety Study

Goal is to assess how well the optimal dose works

Registrational Study (for regulatory authority approval) using Optimal Dose determined from Stage 1

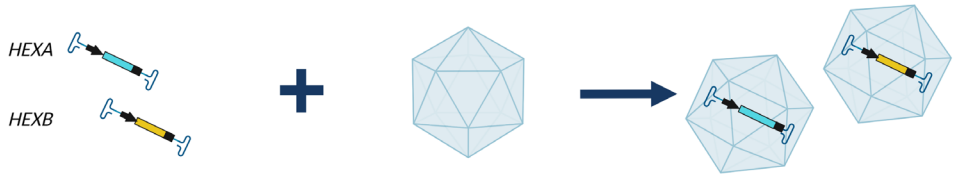
In Stage 1, the first patient enrolled with each dose increase is always a juvenile-onset patient. After each patient is enrolled, a thorough safety evaluation is required before the next patient can be treated. This staggered dosing is included to protect patient safety during this initial stage.

Version 1 approved 06/16/2021

Gene Therapy for GM2 Gangliosidosis (Tay-Sachs and Sandhoff Diseases)

What is AXO-AAV-GM2 gene therapy?

AXO-AAV-GM2 is a liquid that contains working copies of the HEXA and HEXB genes delivered by vectors to cells in the brain and spinal cord. AXO-AAV-GM2 has the potential to slow or stop disease progression.



New, working copies of the *HEXA* gene which is mutated in patients with Tay Sachs disease and *HEXB* gene which is mutated in patients with Sandhoff disease

AAVrh8 vector delivers the genes to cells within the brain and spinal cord

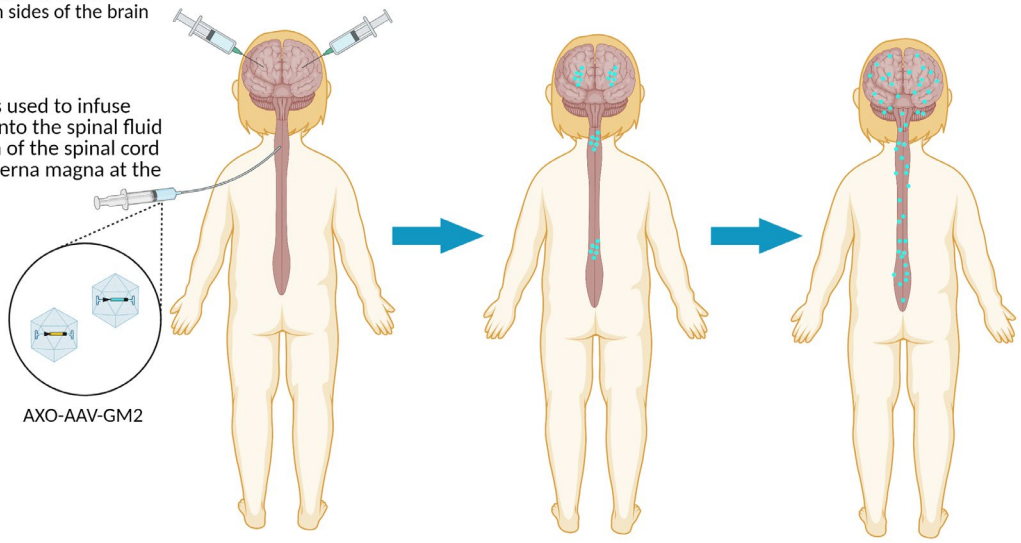
AXO-AAV-GM2 is made up of working copies of *HEXA* and *HEXB* genes placed in AAVrh8 vector

What does the gene therapy procedure involve?

AXO-AAV-GM2 is administered to the brain and spinal cord to allow broad distribution of the therapy.

STEP 1
Infusion of AXO-AAV-GM2 into the thalamus on both sides of the brain

STEP 2:
Microcatheter is used to infuse AXO-AAV-GM2 into the spinal fluid along the length of the spinal cord and into the cisterna magna at the base of the skull



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How long is the study and how often are study assessments conducted?

On-site Screening
~2 months prior to treatment

Administration AXO-AAV-GM2

Frequency of site visits

Month 1	Month 2-3	Month 4-6	Month 7-Year 4	Year 5
weekly	*monthly*	*every 3 months*	*every 6 months*	*yearly*

Infantile-onset: 1-year assessment; 4-year long term follow-up
Juvenile-onset: 2-year assessment; 3-year long term follow-up

Version 1 approved 06/16/2021

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Frequently asked questions

Is my child eligible to participate?

- To assess eligibility for the trial, the study investigators will evaluate many factors. A few of the key eligibility criteria are listed below:
  - ✓ Must have a genetically confirmed diagnosis of Tay-Sachs Disease or Sandhoff disease.
  - ✓ Age at the time of treatment is 6-20 months for infantile-onset patients and 2-12 years for juvenile-onset patients.
  - ✓ Study investigators will also do a series of assessments and discuss other factors with you such as disease severity, surgical readiness, and other medical conditions to ensure the trial is appropriate for your child.

How soon will I need to arrive at the study site to determine study eligibility?

- The study Investigator and their staff will usually do an initial virtual evaluation at least 2 months prior to treatment to determine if your child could be a good candidate for the study. If they determine your child may be suitable for the trial, a coordinator will work with you to arrange travel to the site. The on-site screening to determine study eligibility will begin approximately 1-2 month prior to treatment.
- Enrollment between patients is spaced out to allow sufficient time to assess safety of the administration procedure and the gene therapy prior to dosing another patient. Therefore, even though your child may be determined to be a good candidate, they may not immediately undergo on-site screening.

What assessments are made during the study?

- After receiving AXO-AAV-GM2, your child will have regular follow-up visits at the clinical trial site to assess their health, symptoms and ability to perform various physical and mental tasks. A variety of assessments will be performed including physical exams, MRIs, x-rays, scans, lumbar punctures, and blood draws.
- The main outcome of the trial will be assessed after 1 year of treatment for infantile-onset patients and 2 years of treatment for juvenile-onset patients. Children will then continue to have regular follow-up visits for 3-4 additional years to further evaluate the safety and efficacy (how well it works) of the therapy.

What are the risks and benefits of participating in the trial?

- Participation may help lead to a future treatment. AXO-AAV-GM2 is an experimental treatment that is being tested for the first time in humans. Study participants may or may not benefit from AXO-AAV-GM2 as the treatment benefits have only been demonstrated in animal models at this time.
- There are unknown risks with AXO-AAV-GM2 and the surgical procedure. Children are also required to take immune suppressive medicines to allow gene therapy to work in the body. The study investigator can explain the potential risks associated with this study.

Frequently asked questions (continued)

Does vaccination impact eligibility for the study?

- Vaccinations of any kind are not permitted in the month prior to screening.

Who is conducting the study?

- The study is being conducted in partnership between the University of Massachusetts Medical School and Massachusetts General Hospital under the direction of Dr. Terence Flotte and Dr. Florian Eichler respectively, who work together to provide the treatment and follow-up of the patients enrolled in the trial.

Where will the study take place? What types of travel/accommodation support are provided to families whose child is enrolled in the study?

- Clinical trial visits will be conducted in person at the University of Massachusetts Medical School and Massachusetts General Hospital in Massachusetts in the US. Following AXO-AAV-GM2 administration, patients will need to remain near the study site for approximately 3 months following treatment and will return to the site periodically for five years to undergo various tests and medical exams to continue to monitor safety and efficacy (how well the product works).
- If you are not local to the study site, a company will coordinate your travel and accommodations. Eligible and appropriate expenses incurred while at the study site for clinical trial visits such as flights, accommodations, driving/mileage, tolls/parking, rental cars, public transportation/taxi, meals/food, travel medical insurance will be covered. Details related to the amount covered will be discussed with you at the initial screening visit.

Are patients from outside the US eligible?

- Yes, patients from outside the US are eligible. The first patient enrolled in the trial was from Europe.

Who should I contact if I'm interested in having my child participate in the trial?

- Please discuss the eligibility criteria with your child's physician and for more information, contact the Clinical Research Coordinator at the clinical study site, Haley Andonian at *handonian@partners.org*
- To learn more about AXO-AAV-GM2 or gene therapy, please contact Sio Gene Therapies at *patients@siogtx.com*

Where can I find more information on GM2 gangliosidosis?

- Global patient organizations such as the ones below have many helpful disease related resources.

NTSAD National Tay-Sachs & Allied Diseases Association, Inc.

CTSF Cure Tay-Sachs Foundation

CATS Cure & Action for Tay-Sachs Foundation

Hand in Hand from Tay-Sachs and Sandhoff

ACTAYS Acción y Cura para Tay-Sachs

Rare Find Foundation

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