



National Tay-Sachs &
Allied Diseases Association

Late Onset GM2 (Tay-Sachs & Sandhoff Diseases) Research Day Breakout Session
NTSAD's 47th Annual Family Conference in Dallas
April 25, 2025

The Late Onset GM2 breakout session featured updates from six groups of researchers, and it was moderated by Allison Bradbury, PhD.

Michael Przybilla, PhD, University of Minnesota

Dr. Przybilla submitted a brief video about his research at the University of Minnesota, which focuses on gene therapy and gene editing for lysosomal disorders. He described his work using his proprietary system gene editing (PSG) approach in a mouse model of GM1. His initial research with this gene editing approach had shown that not enough β -gal enzyme was delivered to the brain. In his latest work he uses a β -gal-ApoE fusion enzyme in the GM1 mouse model and shows that β -gal enzyme activity in the brain was increased more than 12 times. In addition, ganglioside levels were normalized in the GM1 mouse brain.

Julie Kissell, PhD candidate at University of Wisconsin

Julie Kissell talked about the development of a disease-specific clinical rating scale for late-onset GM2. As part of the natural history study she and other investigators in the US are running using the rating scale, she is attempting to capture and describe the differences between late-onset Tay-Sachs and Sandhoff diseases. She continues to refine the disease-specific clinical rating scale and hopes it will be valuable for use in future clinical trials. Julie also highlighted the recent publication that describes the first natural history study conducted. It is entitled "Clinical outcome assessments of disease burden and progression in late-onset GM2 gangliosidoses" and it can be accessed here: <https://pubmed.ncbi.nlm.nih.gov/38870773/>. The data for this paper was collected during annual clinical outcome assessments of patients attending the NTSAD Family Conference between 2015 and 2019, and this study characterized the natural history of late-onset GM2 using various clinical outcome assessments.

Sanofi

The Sanofi team sent a video to provide a message from members that were not able to attend the conference. Samantha Walbillic, Global Project Manager Development, Rare Diseases, began by expressing her profound gratitude to all of the patients that participated in the AMETHIST clinical trial using the investigational drug venglustat. Cristina Cardoso, Global Public Affairs Head, Rare Nephrology and Hematology, then acknowledged NTSAD for being an exceptional partner for the

past 10 years and thanked NTSAD for their unwavering support. Next, Riliang Zheng, Clinical Research Director, Rare Diseases, Gaucher and GM2, indicated that the robust data collected is valuable for future research and development purposes. After the video, Julie Kissell, a Sanofi employee, was available to answer questions. Julie noted that the data for this study will be published this year and that there is a process by which investigators can request data. In response to a question regarding the endpoints of the AMETHIST trial, she stated that the clinical endpoint did not show a positive trend.

Heather Gray-Edwards, DVM, PhD, University of Massachusetts Chan Medical School

Dr. Gray-Edwards of UMASS Chan Medical School presented updates on her adeno-associated virus (AAV)-mediated gene therapy work. Her current work is focused on preparing for the next GM2 clinical trial using the second-generation vector which is bicistronic (contains both subunits of the HexA protein). Vector manufacturing is starting in the next three weeks, toxicology studies will begin soon, and all is on schedule for the upcoming GM2 clinical trial. The IND is expected to be ready by the fall, and then the hope is to start enrollment. The main gene therapy side effects seem to be immune responses, and therefore all patients will be on immuno-suppressant therapy. The plan is to treat six infantile patients, three juvenile patients, and three late-onset patients. Heather stated that she expects this clinical trial to start fully in the winter/spring of 2026.

Megan Grosso, Vice President Medical Affairs at IntraBio, Inc.

Megan's presentation focused on IntraBio's drug N-acetyl-L-leucine (IB1001), which was approved in September 2024 by the FDA for the treatment of Niemann Pick disease Type C. IB1001, now called Aqneursa, is the active L-enantiomer of N-acetyl-DL-leucine (Tanganil). This is a small molecule drug that is orally administered. Data from GM2 patients was presented and, although the data look promising, it is not yet approved for GM2. IntraBio has taken multiple steps to try to get approval for the use of Aqneursa in GM2. In April, 2025 the FDA issued a "complete response letter," citing potential for expectation bias and requiring a placebo-controlled trial for GM2. IntraBio has submitted a response letter and are hoping to discuss these issues with them. In addition, they are issuing a GM2 advocacy "Call to Action". NTSAD, Cure-Tay Sachs Foundation, and several global GM2 organizations have initiated an advocacy initiative for individual members of the community to sign on their support, share their personal stories, and request an Advisory Committee of independent experts to review the benefit/risk of AQNEURSA for GM2.

Steven Kushner, MD, PhD, Columbia University, Department of Psychiatry, and SNF Center for Precision Psychiatry & Mental Health

Dr. Kushner is a psychiatrist and a member of the NTSAD Scientific Advisory working group. He is collaborating with Dr. Christopher Stephen, Dr. Camilo Toro, and other members of the NTSAD Scientific Advisory working group that originated at the LOTSS Think Tank meeting sponsored by the Katie & Allie Buryk Fund at NTSAD. The group's initial mandate was to develop care cards for individuals with late onset Tay-Sachs or Sandhoff disease who are experiencing psychiatric

symptoms. These care cards are now available on the NTSAD website. They have recently launched a natural history study aimed at understanding the risk and protective factors related to psychiatric symptoms experienced by LOTSS patients titled *COPING [Comorbid Psychiatric Illness Natural History and Genetics: A Study on Late-Onset Tay-Sachs disease]*. Participants must be 8 years or older and have a confirmed genetic diagnosis of Late-Onset Tay-Sachs or Sandhoff disease. This study involves providing consent for sharing medical records for the team's review, and participating in a psychiatric interview over Zoom. Participants are encouraged to enroll regardless of whether or not they have experienced psychiatric symptoms. For more information, please email Dr. Kushner's research study team at: COPING@cumc.columbia.edu.