Miglustat (Zavesca) and GM1 Gangliosidosis

A Guide for Families

What this is: An honest, plain-language summary of what the research shows about miglustat in GM1, covering the studies that raised hopes, the studies that raised concerns, and what the science actually tells us today.

Who wrote this: This summary was prepared by the CureGM1 Foundation based on published medical research and expert input. It does not replace your child's medical team.

First: What is Miglustat (Zavesca)?

Miglustat is a medication, sold under the brand name **Zavesca**, that was originally designed to slow down the production of certain fatty substances in the body called **gangliosides**.

In GM1 gangliosidosis, the body cannot break down a specific ganglioside called GM1. The idea behind miglustat was: if the body makes *less* of it, maybe it won't pile up so fast. This approach is called **substrate reduction therapy**, or SRT. Think of it as turning down the supply when the drain is blocked.

Important facts to know upfront:

- Miglustat is **FDA-approved** for a different condition called Gaucher disease, and **approved in Europe** for another condition called Niemann-Pick type C (NPC)

- It has **never been approved** for GM1 gangliosidosis; any use in GM1 is off-label
- It has been used in GM1 patients as part of a regimen sometimes called **Syner-G**, usually combined with a ketogenic diet

What Families Often Hear, and What the Research Actually Shows

Many families hear about miglustat from other families, from advocacy groups, or from clinicians who want to offer something when nothing else is available. The hope is completely understandable.

Here is an honest look at what the science says: the encouraging parts and the concerning parts.

The Encouraging Evidence

IN A DIFFERENT DISEASE (NPC), MIGLUSTAT HAS SOLID EVIDENCE

The best evidence for miglustat helping any brain disease comes from **Niemann-Pick type C (NPC)**, a related but different lysosomal storage disease.

- Had **better eye movement control**

- Had **better ability to walk and swallow** compared to patients who didn't take it
- Showed **neurological stabilization**: their condition stayed more stable while untreated patients declined

The approval of miglustat for the treatment of NPC in the EU included the open-label, randomized, non-placebo controlled 12-month trial and on the results of an observational, cohort study. The latter, analysis was retrospective, meaning that after seeing the data the investigators could decide how they would analyze the data, and assessed the effects of miglustat on neurological disease progression who had received treatment off-label.

This was a real, meaningful finding. It's why miglustat is approved for NPC in Europe.

However, NPC is not GM1. The diseases involve different enzymes and different substrates. Evidence in one disease does not automatically transfer to the other.

A SMALL STUDY OF GM1 PATIENTS IN ITALY

In 2020, a group of Italian doctors published a study describing **4 children with GM1 type 2** who were treated with miglustat.

- 3 of the 4 children appeared to have a slower disease course than expected
- The doctors described this as "delayed neurological involvement"

This is meaningful: these were real children and real families.
But it has important limitations:

- It was a very small group (4 patients)

- There was no control group (no comparison to similar children who didn't receive miglustat)

- The doctors acknowledge the study can't prove miglustat caused the improvement

- GM1 type 2 naturally varies a lot from child to child

This kind of study is called **hypothesis-generating**: it's enough to say "this might be worth studying further," but not enough to say "this treatment works."

The Concerns the Science Raises

CONCERN 1: THE MEDICATION MAY NOT BE DOING WHAT WE THOUGHT

Here is one of the most striking scientific findings, and it comes from two independent research teams.

When scientists gave miglustat to mice with Sandhoff disease and NPC (two related diseases), the mice did better: they lived longer and moved better. **But something unexpected happened:** the fatty substance that was supposed to decrease in the brain *actually increased.*

Think of it like this: imagine you try to unclog a sink by turning off the faucet, but somehow the sink fills up *faster* with the faucet turned off. That tells you the faucet wasn't the real problem, and turning it off isn't how you're fixing things.
- What this means: the researchers concluded that **miglustat is probably helping through a completely different mechanism** than originally intended. It appears to block a different enzyme (called NLGase, which is also knows as GBA2) rather than the one it was designed to target.

GBA2, is the gene than encodes the non-lysosomal glucocerebrosidase (NLGase). NLGase is the correct name, but it is often referred to in the literature as "GBA2", so for the purpose of this summary we will keep with the older terminology and use GBA2 when we speak of the enzyme.

This matters because:

- The benefit may be coming from something we don't fully understand yet
- This different mechanism also comes with risks (more on that below)
- Better-targeted drugs aimed at this same mechanism may work more safely in the future

CONCERN 2: THE MEDICATION DOES NOT EASILY CROSS INTO THE BRAIN

The brain is protected by something called the **blood-brain barrier**, which filters out most substances to protect the brain from harmful compounds. Miglustat only reaches the brain in very small amounts, roughly **one-tenth of what is in the bloodstream**.

For GM1, where the disease is primarily in the brain, this is a significant limitation. The drug may not be reaching the affected area in meaningful amounts.

CONCERN 3: THE MOUSE STUDIES IN GM1 WERE INCONSISTENT

The most important GM1 mouse study (published in 2008) found some early benefits (less ganglioside buildup, calmer brain inflammation, better early movement), but **the mice treated with miglustat died at the same time as untreated mice.** There was no survival benefit in GM1 mice.

There is also a methodological concern: mice on miglustat eat less because the medication causes nausea and GI upset. Eating less itself can sometimes slow disease progression in animal models. The study didn't account for this difference, which means the benefits seen in mice might partly be from eating less, not from the drug itself.

CONCERN 4: SIDE EFFECTS ARE SIGNIFICANT

Miglustat has real side effects, and they are common:

- **Stomach problems** (diarrhea, cramping, bloating): more than 70% of patients experience these
- **Weight loss**: concerning especially in growing children who need good nutrition
- **Possible nerve effects**: long-term use has been associated with worsening of coordination or nerve symptoms in some patients, which is especially concerning in children who already have neurological disease
- In Gaucher disease, where the most data exist, approximately **85% of patients eventually stop taking miglustat** because of side effects, far more than other comparable medications

CONCERN 5: THE SYNER-G COMBINATION IS HARD TO EVALUATE

Some families have used miglustat as part of a "Syner-G" regimen with a ketogenic diet. The ketogenic diet has its own benefits for neurological conditions. When the two are used together, it's impossible to know from existing data whether any improvement comes from the miglustat, the diet, or both together.

There are no controlled studies separating these effects.

What Does This All Add Up To?

Here is an honest summary:

Question	What the evidence says
Does miglustat work well in NPC?	**Yes.** Real clinical trial evidence supports it.
Does miglustat work in GM1?	**Unknown.** Small case series, no controlled trials.
Do animal studies support it for GM1?	**Weakly.** Benefits in related diseases, but not in GM1 mice specifically; caloric restriction concern.
Is the mechanism we thought correct?	**Likely not.** The drug appears to work through a different pathway than intended.
Are the side effects real?	**Yes.** GI side effects are very common; neurological risks are mechanistically plausible.
Is it wrong to have tried it?	**No.** Families and doctors made reasonable decisions with the information available.

What This Means Going Forward

IT IS SCIENTIFICALLY SOUND TO STOP MIGLUSTAT

If a child has been on miglustat and their family or medical team is considering stopping, the science supports that decision. There is no strong evidence that stopping miglustat will cause deterioration, and the side effect burden is real.

This does not mean the families who used it made a mistake. They were working with the best information available at the time, and they were trying everything possible to help their children. That is love, and it is right.

WHAT WE KNOW ABOUT VENGLUSTAT IN GM1 PATIENTS (AMETHIST TRIAL, 2026)

A drug called **venglustat** (made by Sanofi/Genzyme) was tested in a large study called the **AMETHIST trial**. Unlike miglustat, venglustat is very good at getting into the brain which is exactly where GM1 causes damage.

The AMETHIST trial enrolled two groups of patients:

- **A large group of GM2 patients** (a related disease) in a proper controlled trial

- **A small group of 7 GM1 patients** in an open-label arm, treated for up to two years

What the 7 GM1 patients showed:

The researchers measured a specific substance in the spinal fluid (CSF) called GM1 ganglioside the very substance that builds up in GM1 gangliosidosis. After two years on venglustat:

- **GM1 levels in the spinal fluid dropped by 29%** (on average)
- A related substance called glucosylceramide dropped even more by **70%**
- Tests of hand coordination and walking showed modest improvement or remained stable
- Quality of life was stable

These are genuinely encouraging findings. It is the **first time** any drug has been shown to reduce GM1 ganglioside in the spinal fluid of GM1 patients.

Important caveats families should know:

- There were only 7 patients a very small group
- There was **no comparison group** (no patients who received a placebo/dummy pill), so we cannot be certain the drug caused the improvements
- One child, who was 2 years old when the study began, sadly died before the end of the study from disease progression not from the drug
- These results are a **proof of concept**, not proof of treatment effectiveness

What happened in the GM2 group tells us something important:

In the larger GM2 patient group, venglustat also successfully reduced ganglioside levels in the spinal fluid by nearly 50%. But it produced **no measurable clinical benefit**: patients on venglustat did no better than patients on placebo in tests of hand function and coordination. The biochemistry worked; the clinical benefit did not follow.

This is actually an important scientific finding: reducing ganglioside levels in the brain may not be enough on its own. It suggests the more important target may be a different enzyme (called GBA2) which is what miglustat also happens to affect, and which the next-generation drug **nizubaglustat** (currently in a Phase 3 clinical trial) is designed to target more precisely, and with genuinely effective brain penetration.

The bottom line for families:

The AMETHIST GM1 data are the most encouraging recent findings in this space real human data showing that a drug can actually reduce GM1 in the spinal fluid. But we need more research, in more patients, with a comparison group, to know whether that reduction translates into clinical benefit for children with GM1.

NIZUBAGLUSTAT: A DRUG DESIGNED FOR THIS MECHANISM IS NOW IN PHASE 3

The scientific insight from miglustat that the GBA2 enzyme pathway matters in GM1 has directly shaped a next-generation drug that is now in an active Phase 3 clinical trial.

Nizubaglustat (also called AZ-3102, made by Azafaros, a Dutch biotech company) was specifically designed to:

- Cross into the brain effectively (which requires lower doses to reach effective concentrations in the brain)
- Target both the GCS and GBA2 pathway in a balanced and very potent manner
- Allow for once-a-day dosing
- Avoid the severe stomach side effects that make miglustat so hard to tolerate

What has the research shown so far?

- In a Phase 1 study in healthy adults, nizubaglustat was confirmed to reach the brain measured directly in spinal fluid
- Animal studies in related diseases (GM2 and Niemann-Pick type C) showed improved survival and reduced brain inflammation
- Azafaros reports benefit in GM1, GM2, and Niemann-Pick type C animal models
- A Phase 2 study (called RAINBOW) enrolled 13 patients with GM2 and Niemann-Pick C and reported positive safety results in 2024. This research will be published soon.

The Phase 3 trial (NCT07082543) is now enrolling:

- **Who can participate:** patients with GM1 gangliosidosis, GM2 gangliosidosis, or Niemann-Pick type C, aged 4 and older
- **Duration:** 18 months, randomized and placebo-controlled

- **Regulatory status:** FDA has granted Orphan Drug designation, Rare Pediatric Disease designation, and Fast Track status for all three diseases

This is the most clinically advanced drug candidate currently targeting the biological pathway that miglustat engages and the only one in a pivotal trial that includes GM1 patients.

A research compound called sinbaglustat also confirmed the GBA2 pathway in GM1 mice (2025 study), but was not moved into clinical development by the company that created it. Its contribution is as scientific evidence, not a treatment path.

OTHER APPROACHES IN GM1 RESEARCH AND DEVELOPMENT

In addition to the drug approaches described above, other treatment strategies for GM1 are under active development:

- **Enzyme replacement therapy (ERT)** delivered directly into the brain or spinal fluid, which addresses the underlying enzyme deficiency directly
- **Gene therapy** approaches aimed at correcting the genetic defect in brain cells
- Improved **seizure management** and **supportive care** that can meaningfully improve quality of life

The CureGM1 Foundation is actively engaged in advancing enzyme replacement therapy for GM1.

Questions to Ask Your Child's Doctor

If you are currently using miglustat, or considering it, here are some questions that may be helpful:

- "Is my child currently experiencing any of the known side effects of miglustat?"
- "What would we look for to know whether the medication is helping?"
- "If we stopped miglustat, what would we watch for?"
- "Are there any clinical trials my child might qualify for?"
- "What is your view on the Syner-G approach given the newer evidence about how miglustat works?"

The Research Behind This Guide

This summary is based on nine published studies. If you would like to read them or share them with your medical team, they are listed here:

1. Ashe et al. (2011): Mouse study of Sandhoff disease. Found survival benefit but brain fatty substance *increased*, not decreased. PLoS ONE. pubmed.ncbi.nlm.nih.gov/21738789
2. Nietupski et al. (2012): Mouse study of NPC. Same paradox: benefit despite brain GM1 going up. Mol Genet Metab. pubmed.ncbi.nlm.nih.gov/22366055
3. Shayman & Larsen (2014): Expert review showing miglustat is ~60x more potent at a different enzyme (GBA2) than its intended target. J Lipid Res. pubmed.ncbi.nlm.nih.gov/24534703
4. Elliot-Smith et al. (2008): GM1 mouse study. Early biochemical benefits, but no survival benefit. Mol Genet Metab. pubmed.ncbi.nlm.nih.gov/18387328
5. Fischetto et al. (2020): Italian study of 4 children with GM1 type 2. Apparent slowing of disease, but small and uncontrolled. Mol Genet Genomic Med. pubmed.ncbi.nlm.nih.gov/32779865
6. Patterson et al. (2007): Randomized controlled trial in NPC. Real evidence of neurological stabilization. Lancet Neurol. pubmed.ncbi.nlm.nih.gov/17689147
7. Wraith et al. (2010): Long-term follow-up of NPC patients on miglustat. Continued stabilization at 24 months. Mol Genet Metab. pubmed.ncbi.nlm.nih.gov/20045366
8. Geberhiwot et al. (2018): European clinical guidelines for NPC management. Supports miglustat for NPC neurological stabilization. Orphanet J Rare Dis. pubmed.ncbi.nlm.nih.gov/29625568
9. Wannemacher et al. (2025): Sinbaglustat confirmed the GBA2 pathway in GM1 mice; the compound was shelved and not advanced to clinical trials. Neurobiol Dis. pubmed.ncbi.nlm.nih.gov/40250720
10. Paquet Luzy C et al. (2024): First-in-human study of nizubaglustat; confirmed brain penetrance in healthy adults. Mol Genet Metab. pubmed.ncbi.nlm.nih.gov/38113551
11. Landskroner K et al. (2026): Therapeutic effects of nizubaglustat in a GM2 mouse model extended survival and reduced neuroinflammation. J Inherit Metab Dis. pubmed.ncbi.nlm.nih.gov/41500827

A Word to Families

Navigating a GM1 diagnosis, whether for your child or a loved one, is one of the hardest things a family can face. When treatments are scarce and the stakes are everything, it makes complete sense to search for every possible option.

The goal of this guide is not to take hope away. It is to give you the most accurate picture possible so you can make decisions with your medical team from a place of real understanding rather than uncertainty.

The science on GM1 is advancing. The community of researchers, families, and advocates working on this disease is growing. You are not alone in this.

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This document does not constitute medical advice. Always discuss treatment decisions with your child's medical team.