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.

What changed in version 2. We corrected two things this guide got wrong. Version 1 said miglustat barely reaches the brain; the drug's own FDA label shows it crosses into the brain perfectly well, and the real problem is different, so Concern 2 has been rewritten. Version 1 also gave side effect figures we could not trace to a source, including a claim that about 85% of Gaucher patients stop the drug. Those are replaced with the figures published in the FDA label, which are *higher* than the ones we had printed. We have also updated the Phase 3 trial details, which changed after version 1 went out.

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, type 1 Gaucher disease, in adults for whom enzyme replacement therapy is not an option,[1] and **approved in Europe** for another condition called Niemann-Pick type C (NPC)[2]
- 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. In a randomized controlled trial, patients who took miglustat:[3]

- 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[3][4]

The European approval of miglustat for NPC rested on two things: a 12-month trial that was randomized but open-label and had no placebo group, and a separate observational cohort study.[2][3] That second study was retrospective, meaning the investigators could decide how to analyse the data after they had already seen it, and it looked at patients who had received miglustat off-label.

This was a real, meaningful finding. It is why miglustat is approved for NPC in Europe.[2]

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.[5]

- 3 of the 4 children appeared to have a slower disease course than expected[5]
- The doctors described this as “delayed neurological involvement”[5]

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, meaning no comparison to similar children who did not receive miglustat
- The doctors acknowledge the study can't prove miglustat caused the improvement[5]
- GM1 type 2 naturally varies a lot from child to child

This kind of study is called **hypothesis-generating**: it is 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.[6][7]

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.[6][7]

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 was not the real problem, and turning it off is not how you are 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, rather than the one it was designed to target.[8]

NLGase is encoded by a gene called GBA2. NLGase is the correct name for the enzyme, but the literature usually calls it GBA2, so for the rest of this guide we will use GBA2 too.

This matters because:

- The benefit may be coming from something we do not fully understand yet
- This different mechanism also comes with risks, covered below
- Better-targeted drugs aimed at this same mechanism may work more safely in the future

CONCERN 2: THE AMOUNT THAT REACHES THE BRAIN IS NOT ENOUGH TO DO THE JOB IT WAS DESIGNED FOR

Miglustat does get into the brain. Measured directly in spinal fluid, it reaches somewhere between about a third and two thirds of the level in the bloodstream.[1] Crossing the blood-brain barrier is not the problem.

The problem is what the drug does once it is there. At the doses a person can actually tolerate, miglustat blocks GBA2 roughly 60 times more strongly than it blocks the enzyme it was designed to block.[8] To turn down ganglioside production in the brain, the dose would have to be far higher than anyone can take.

For GM1, this means the intended effect, less GM1 being made, is not what the drug is doing in the brain at any real-world dose. Whatever effect it does have is coming from somewhere else, which is exactly what Concern 1 describes.

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.[9]

There is also a methodological concern. Mice on miglustat eat less, because the medication causes nausea and stomach upset. Eating less can itself slow disease progression in animal models. The study did not account for this difference, which means the benefits seen in mice might partly come from eating less rather than from the drug.[9]

CONCERN 4: SIDE EFFECTS ARE SIGNIFICANT

Miglustat has real side effects, and they are common. The figures below come from the Gaucher disease trials behind the drug's FDA label, which is where the most complete safety data exist.[1]

- Stomach problems (diarrhea, cramping, bloating): diarrhea was reported in 89 to 100% of patients[1]
- Weight loss: reported in 39 to 67% of patients,[1] which is a particular worry in growing children who need good nutrition
- Possible nerve effects: tremor was reported in 11 to 17% of patients, and peripheral neuropathy has been reported with long-term use.[1] This is especially concerning in children who already have neurological disease
- **Stopping because of side effects:** tremor and diarrhea are the reactions most often requiring a dose change or a stop.[1] In Gaucher disease, where the most data exist, many patients eventually come off miglustat, and the stomach effects are the usual reason

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 is 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, and there is a caloric restriction concern.
Is the mechanism we thought correct?	Likely not. The drug appears to work through a different pathway than intended.
Does enough of it reach the brain to work as designed?	It does reach the brain, but not at a dose that produces the intended effect.
Are the side effects real?	Yes. Stomach side effects are near-universal; 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

STOPPING MIGLUSTAT: HOW WE READ THE EVIDENCE

If a child has been on miglustat and their family or medical team is considering stopping, here is how the CureGM1 Foundation reads the evidence.

No study has followed what happens to children with GM1 when miglustat is stopped. That means nobody can tell you with certainty what to expect, and anyone who says otherwise, in either direction, is going beyond the evidence.

What we can say is this. The case for benefit in GM1 rests on small uncontrolled series, and the side effect burden is real and measurable. Weighing those against each other, we think the decision to stop is scientifically defensible. It is a decision to make with your child's medical team, and our full reading of the evidence is set out in the companion Scientific Research Series report.

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.[10]

The AMETHIST trial enrolled two groups of patients:[10]

- 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 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%[10]
- A related substance called glucosylceramide dropped even more, by 70%[10]
- Tests of hand coordination and walking showed modest improvement or remained stable[10]
- Quality of life was stable[10]

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.[10]

Important caveats families should know:

- There were only 7 patients, a very small group[10]
- There was no comparison group, no patients who received a placebo, 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[10]
- 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.[10]

This is an important scientific finding in its own right: reducing ganglioside levels in the brain may not be enough on its own. It suggests the more important target may be a different enzyme, GBA2, which is what miglustat also happens to affect, and which the next-generation drug nizubaglustat is designed to target more precisely and with genuinely effective brain penetration.[8][10]

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 IN PHASE 3

The scientific insight from miglustat, that the GBA2 enzyme pathway matters in GM1, has directly shaped a next-generation drug 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 allows lower doses to reach effective concentrations in the brain
- Target both the GCS and GBA2 pathways in a balanced and very potent manner
- Allow 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[11]
- Animal studies in a related disease, GM2, showed improved survival and reduced brain inflammation[12]
- Azafaros states that nizubaglustat is the only drug in development showing neurological improvement in all three preclinical models: GM1, GM2 and Niemann-Pick type C.[13] The GM1 animal data behind that statement have not been published on their own, so it rests on the company's account rather than on a paper anyone can read
- A Phase 2 study called RAINBOW (NCT05758922) enrolled 13 patients with GM2 gangliosidosis or Niemann-Pick type C. It has now completed, and the full results, covering safety and clinical outcomes through 18 months, were published in 2026[14]

The Phase 3 trial (NCT07082543) is active but no longer recruiting. Enrollment closed at 75 participants:[15]

- Who was eligible: patients with GM1 gangliosidosis or GM2 gangliosidosis, aged 4 and older[15]
- Duration: 18 months, randomized, double-blind and placebo-controlled[15]
- Regulatory status: FDA has granted Orphan Drug designation, Rare Pediatric Disease designation and Fast Track status for GM1 gangliosidosis, GM2 gangliosidosis and Niemann-Pick type C[16]

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 in a 2025 study, but was not moved into clinical development by the company that created it.[17] 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 guide is based on the sources listed below. The numbers in the text point here. If you would like to read them or share them with your medical team, every entry carries an identifier you can search on.

1. **Zavesca (miglustat) US prescribing information.** The official FDA-approved drug label. This is the source for what miglustat is approved to treat, for how much of it reaches the brain, and for the side effect rates quoted in this guide. Actelion Pharmaceuticals US, Inc., Titusville (NJ); revised August 2022. dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=817892d1-ee12-4632-85fc-57ccdf16d7b8 Accessed August 14, 2026.
2. **Geberhiwot et al. (2018):** European clinical guidelines for Niemann-Pick type C management. Supports miglustat for neurological stabilization in NPC. *Orphanet J Rare Dis.* doi:10.1186/s13023-018-0785-7. PMID 29625568.
3. **Patterson et al. (2007):** Randomized controlled trial in NPC. Real evidence of neurological stabilization. *Lancet Neurol.* doi:10.1016/S1474-4422(07)70194-1. PMID 17689147.
4. **Wraith et al. (2010):** Long-term follow-up of NPC patients on miglustat. Continued stabilization at 24 months. *Mol Genet Metab.* doi:10.1016/j.ymgme.2009.12.006. PMID 20045366.
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.* doi:10.1002/mgg3.1371. PMID 32779865.

6. **Ashe et al. (2011):** Mouse study of Sandhoff disease. Found a survival benefit, but the fatty substance in the brain increased rather than decreased. *PLoS ONE.* doi:10.1371/journal.pone.0021758. PMID 21738789.

7. **Nietupski et al. (2012):** Mouse study of Niemann-Pick type C. The same paradox: benefit despite brain glucosylceramide going up. *Mol Genet Metab.* doi:10.1016/j.ymgme.2012.01.020. PMID 22366055.

8. **Shayman & Larsen (2014):** Expert review showing miglustat is roughly 60 times more potent at a different enzyme (GBA2) than at its intended target. *J Lipid Res.* doi:10.1194/jlr.R047167. PMID 24534703.

9. **Elliot-Smith et al. (2008):** GM1 mouse study. Early biochemical benefits, but no survival benefit. *Mol Genet Metab.* doi:10.1016/j.ymgme.2008.02.005. PMID 18387328.

10. **Tifft CJ, Batsu I, Giugliani R, et al. (2026):** Venglustat in GM2 gangliosidoses and related disorders: results of the AMETHIST randomized controlled and basket trials. *Genet Med.* 2026;28(1):101615. doi:10.1016/j.gim.2025.101615. PMID 41108138.

11. **Paquet Luzy et al. (2024):** First-in-human study of nizubaglustat; confirmed brain penetrance in healthy adults. *Mol Genet Metab.* doi:10.1016/j.ymgme.2023.108113. PMID 38113551.

12. **Landskroner et al. (2026):** Therapeutic effects of nizubaglustat in a GM2 mouse model; extended survival and reduced brain inflammation. *J Inherit Metab Dis.* doi:10.1002/jimd.70130. PMID 41500827.

13. **Azafaros B.V. (2026):** Azafaros announces publication of preclinical efficacy data with nizubaglustat in GM2 gangliosidosis [press release]. Leiden (NL); February 25, 2026. This is the company statement, not a published paper. azafaros.com/news-media/azafaros-announces-publication-of-preclinical-efficacy-data-with-nizubaglustat-in-gm2-gangliosidosis/l264c14 Accessed August 14, 2026.

14. **López de Frutos L, do Valle DA, Horovitz DDG, et al. (2026):** The RAINBOW study: a phase 2 trial of nizubaglustat in GM2 gangliosidoses or Niemann-Pick type C disease, reporting pharmacokinetic data at 3 months and clinical and safety outcomes through 18 months. *Mol Genet Metab.* 2026;148(4):110164. doi:10.1016/j.ymgme.2026.110164.

15. **Azafaros B.V.** A study to evaluate the safety and efficacy of oral nizubaglustat (AZ-3102) in late-infantile and juvenile forms of GM1 gangliosidosis or GM2 gangliosidosis. ClinicalTrials.gov identifier NCT07082543. clinicaltrials.gov/study/NCT07082543 Active, not recruiting; status checked August 14, 2026.

16. **Azafaros B.V. (2026):** Azafaros completes enrollment of Phase 3 (NAVIGATE) study evaluating nizubaglustat for the treatment of patients with GM1/GM2 gangliosidoses [press release]. Leiden (NL); July 23, 2026. azafaros.com/news-media/azafaros-completes-enrollment-of-phase-3-navigate-study-evaluating-nizubaglustat-for-the-treatment-of-patients-with-gm1-gm2-gangliosidoses/l280c14 Accessed August 14, 2026.

17. **Wannemacher et al. (2025):** Sinbaglustat confirmed the GBA2 pathway in GM1 mice; the compound was shelved and never advanced to clinical trials. *Neurobiol Dis.* doi:10.1016/j.nbd.2025.106917. PMID 40250720.

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.