Miglustat (NB-DNJ / Zavesca) in GM1 Gangliosidosis and Related Lysosomal Storage Diseases

An Objective Research Landscape Report

Purpose: Objective synthesis of evidence arguing both for and against miglustat's benefit in GM1 and related conditions, with frank assessment of what the science does and does not support.

Scope: Preclinical (mouse and cell) models, clinical series, and expert commentary through August 2026.

> **What changed in version 2.** Section 4.1 previously reported gastrointestinal toxicity as occurring in ">70% of patients in clinical trials" and referred to a high but unquantified discontinuation rate in Gaucher disease. The figures are now taken directly from the Zavesca US prescribing information, which reports higher rates than the version 1 text did. No published source for a specific discontinuation percentage could be located, so none is given. The Phase 3 and RAINBOW trial descriptions in Part VI are updated to their August 2026 status, and the RAINBOW results now cite the full publication rather than a conference topline. References are numbered identically across this report, the companion Family Resource Series guide, and the Miglustat page on curegm1.org, so a given number is the same source in all three.

Background: What Miglustat Is and What It Was Supposed to Do

Miglustat (N-butyldeoxynojirimycin; NB-DNJ; brand name Zavesca) is a small molecule originally developed as substrate reduction therapy (SRT) for lysosomal storage diseases. The theoretical rationale: if the lysosomal enzyme that clears a substrate is absent or deficient, then partially blocking the upstream enzyme that makes that substrate should reduce the accumulation burden.

For GM1 gangliosidosis, β-galactosidase (GLB1) is absent or deficient, so the intended target was the upstream enzyme **glucosylceramide synthase (GCS)**, which initiates the glycosphingolipid synthesis pathway. Blocking GCS would theoretically reduce synthesis of the entire ganglioside family (GM3, GM2, GM1 and others) and allow any residual GLB1 to remove excess gangliosides.

Miglustat is **FDA-approved for type 1 Gaucher disease** (2003), as monotherapy in adults with mild to moderate disease for whom enzyme replacement therapy is not a therapeutic option,[1] and **EMA-approved for Niemann-Pick type C** neurological manifestations (2009) in adults and children for whom enzyme replacement therapy is not suitable.[2] It has **never been approved for GM1 gangliosidosis**. Its use in GM1 is entirely off-label, including the Syner-G regimen.

Part I: The Case Against Miglustat in GM1, the Pharmacological Critique and Preclinical Evidence

1.1 MIGLUSTAT DOES NOT REACH THERAPEUTIC CONCENTRATIONS IN THE BRAIN, BUT NOT BECAUSE OF THE BLOOD-BRAIN BARRIER

A core pharmacological objection to miglustat in GM1 is concentration-dependent, and it is frequently misstated. **The blood-brain barrier does not substantially block CNS penetration of miglustat.** Cerebrospinal fluid concentrations have been measured at 31.4 to 67.2% of simultaneous plasma levels, and the US label states plainly that this indicates miglustat crosses the blood-brain barrier.[1]

The critical pharmacological concern is concentration-versus-selectivity. At the plasma concentrations achieved clinically, miglustat inhibits **GBA2** (non-lysosomal glucosylcerebrosidase) approximately 60-fold more potently than it inhibits GCS.[8] To achieve the intended substrate reduction effect in the CNS, far higher concentrations would be needed than are achievable clinically.

This is not a theoretical concern. Two independent preclinical studies conducted at Genzyme/Sanofi documented exactly this paradox:

ASHE ET AL. (2011), SANDHOFF DISEASE (HEXB-NULL) MOUSE MODEL

- Miglustat (NB-DNJ) improved motor performance, reduced neuroinflammation, and extended lifespan by roughly 34 to 41%[6]
- However, brain glucosylceramide (GlcCer, also known as GL1) **increased more than 20-fold** in treated animals[6]
- Brain GM2, the substrate that accumulates in Sandhoff, was not meaningfully reduced[6]
- A second-generation GCS inhibitor (Genz-529468) with better CNS penetration replicated the survival benefit but also paradoxically increased brain GlcCer[6]
- **Conclusion of the authors:** the observed CNS benefit is inconsistent with GCS inhibition as the mechanism; “the most likely explanation is inhibition of GBA2”[6]

GBA2 is the gene encoding non-lysosomal glucocerebrosidase (NLGase). NLGase is the correct name for the enzyme, but the literature commonly uses GBA2, and this report follows that convention. The enzyme acts mostly in the brain, where it converts GlcCer to ceramide. Inhibiting it therefore raises brain GlcCer.

NIETUPSKI ET AL. (2012), NIEMANN-PICK C (NPC1-NULL) MOUSE MODEL

- Miglustat improved motor function, reduced CNS inflammation, and extended survival by roughly 30 to 40%[7]
- Brain GlcCer increased approximately 3-fold in treated mice, exactly the opposite of what GCS inhibition would produce[7]
- Liver GlcCer fell as expected, confirming that peripheral GCS inhibition was occurring, while brain GlcCer rose[7]
- CD68+ macrophage infiltration in the liver was unchanged despite substrate reduction there[7]
- **Conclusion of the authors:** “GBA2 inhibition, rather than inhibition of GlcCer synthesis, is likely responsible for the beneficial effects of NB-DNJ in the NPC1 mouse model”[7]

SHAYMAN & LARSEN (2014) REVIEW

- Comprehensive survey of small molecule SRT inhibitors for lysosomal storage diseases[8]
- On selectivity: miglustat inhibits GBA2 at concentrations roughly 60-fold lower than those required to inhibit GCS[8]

- At typical plasma concentrations in treated patients, GBA2 inhibition is the dominant pharmacological effect[8]
- Additional off-target enzymes inhibited at clinically relevant concentrations include intestinal disaccharidases (sucrase, maltase, isomaltase), glycogen debranching enzyme, and lysosomal GBA (acid β-glucosidase)[8]

1.2 THE CALORIC RESTRICTION CONFOUND IN GM1 MOUSE STUDIES

The Oxford group's studies in β-galactosidase-null (GM1) mice are frequently cited as the primary preclinical justification for miglustat in GM1.[9] These studies documented biochemical improvements and behavioral preservation in treated animals. A methodological objection substantially undermines their interpretation:

- Miglustat causes significant gastrointestinal toxicity (diarrhea, cramping, nausea, weight loss) via disaccharidase inhibition in the gut[8][1]
- Treated animals therefore eat less and lose weight. This is caloric restriction by a non-specific mechanism
- Multiple murine LSD models respond to caloric restriction alone, independent of any specific treatment effect
- The Oxford studies were **not pair-fed**. Control animals ate *ad libitum* while treated animals were effectively on a caloric-restricted diet[9]
- Caloric intake was never formally measured or reported[9]
- Without pair-feeding controls, it is impossible to distinguish a disease-specific therapeutic effect from a non-specific caloric restriction effect

This methodological gap has not been directly addressed in the published GM1 mouse literature. It is not a minor concern. It potentially explains the entire apparent benefit.

1.3 THE GM1 MOUSE DATA ARE WEAK EVEN ON THEIR OWN TERMS

Elliot-Smith et al. (2008), the most-cited GM1 mouse study, reported the following in β-gal-null mice treated with NB-DNJ from birth:[9]

- Reduced GM1 and GA1 ganglioside accumulation in brain at 15 weeks
- Normalized endocytic recycling
- Reduced microglial activation
- Maintained rearing behavior through 15 weeks

What was not observed:

- Extended survival. Treated mice died at the same time as untreated controls, which the authors attribute partly to severe rectal prolapse from GI toxicity[9]
- Persistence of benefit. The study endpoints at 15 weeks captured early-course animals, and the behavioral benefit did not persist to later timepoints
- Any parallel to the Sandhoff and NPC models, where survival extension *was* observed[6][7]

For GM1 specifically, therefore, the animal data show: (a) some early biochemical effects, (b) no survival benefit, (c) severe GI toxicity, and (d) a likely caloric restriction confound.

1.4 STRUCTURAL UNSUITABILITY OF SRT FOR COMPLETE ENZYME LOSS

Shayman & Larsen make a theoretical point that applies directly to infantile and severe GM1: substrate reduction therapy is designed for conditions of *partial* enzyme deficiency, where residual enzyme activity can clear substrate once production is reduced.[8] For conditions with near-complete or complete enzyme loss, as in infantile GM1 with pathogenic variants, reducing the substrate synthesis rate does not help, because there is essentially no enzymatic clearance to augment. The substrate accumulates regardless.

Juvenile-onset (type 2) patients, who retain some residual enzyme activity as evidenced by their later presentation, are in a theoretically different category. Even for them, the preclinical rationale remains substantially undermined by the mechanistic evidence above.

Part II: The Case For Miglustat, What the Supporting Literature Claims

2.1 NIEMANN-PICK TYPE C: THE STRONGEST EVIDENCE

The most robust evidence for miglustat in a CNS lysosomal storage disease is in NPC, where the drug has regulatory approval in Europe and is widely used.

Patterson et al. (2007), randomized controlled trial (n=29):[3]

- Patients with NPC, 12 years and older, ambulatory, randomized to miglustat versus supportive care
- Primary endpoint: horizontal saccadic eye movement velocity, significantly improved in the treated group when patients taking benzodiazepines were excluded (p=0.028)
- Secondary endpoints: ambulation, swallowing and cognition stabilized in treated patients versus decline in controls
- Interpretation: meaningful neurological stabilization over 12 months

A non-controlled open-label extension of the original trial reported continued neurological stabilization in adult and juvenile NPC patients over 24 months of miglustat therapy.[4] Consensus clinical management guidelines synthesizing multicenter European registry experience likewise support neurological stabilization as the primary documented benefit in appropriately selected NPC patients.[2]

Key caveat. The mechanism of benefit in NPC is also not fully understood, and the underlying pathophysiology is very different from GM1. In NPC the defect is in a transporter; in GM1 it is in a lysosomal enzyme. The Nietupski 2012 study, which showed brain GlcCer rising despite functional benefit in NPC mice, suggests that even in NPC miglustat is not acting through its intended GCS-inhibition mechanism.[7] The observed benefit may be real while the explanation of why is wrong. This does not invalidate the clinical evidence, but it does mean the theoretical framework for using miglustat cannot be exported cleanly from NPC to GM1.

2.2 SMALL CLINICAL SERIES IN GM1

Fischetto et al. (2020), multicenter Italian cohort, pediatric GM1 type 2 patients:[5]

- The most frequently cited clinical evidence for miglustat benefit in GM1
- Patients treated with miglustat reported as having delayed neurological involvement compared to natural history
- Methodology: retrospective, uncontrolled case series; no control arm; small sample size; comparison to historical controls with inherent selection bias
- Outcome assessment: largely qualitative clinician impressions and caregiver reports

- Limitations acknowledged by the authors: no randomization, no blinding, substantial heterogeneity in dose, duration and timing of initiation, no biomarker endpoints

This study is hypothesis-generating at best. It does not constitute evidence of efficacy by the standards applied to drug approval.

Several case reports and small series from Italy, Turkey and France have similarly described patients with GM1 type 2 who appeared to have a prolonged or stable course during miglustat therapy. In each case the interpretation is confounded by: (a) the wide natural variability in GM1 type 2 course, (b) lack of control groups, (c) the simultaneous use of other interventions, ketogenic diet in many, and (d) observational or retrospective design.

2.3 GM2 GANGLIOSIDOSIS (TAY-SACHS / SANDHOFF) CLINICAL EXPERIENCE

Formal clinical trials of miglustat in GM2 gangliosidosis were conducted in the early 2000s. These yielded limited success: some patients with later-onset disease appeared to stabilize, while infantile-onset patients did not benefit. The trials were small and lacked statistical power. This experience is relevant context but does not translate directly to GM1, because the substrate, enzyme and biology differ.

2.4 THE SYNER-G RATIONALE

The Syner-G protocol, combining miglustat with a ketogenic diet, was proposed on the rationale that ketosis independently alters neuronal metabolism and may have neuroprotective effects additive with SRT. The theoretical basis has biological plausibility: ketogenic diets independently reduce glycolytic flux and may reduce ganglioside synthesis substrate availability. However:

- There is no controlled study separating ketogenic diet effects from miglustat effects in GM1, and the proposed mechanism by which a ketogenic diet reduces ganglioside synthesis is theoretical
- Clinical reports of the Syner-G regimen are anecdotal and retrospective
- It is not possible from existing data to attribute any observed benefit to the miglustat component specifically, rather than to ketogenic diet, natural disease variability, or placebo and ascertainment effects

Part III: Mechanism Revisited, What GBA2 Inhibition Actually Means

The preclinical studies converge on a striking mechanistic revision: the CNS effects of miglustat in LSD mouse models are most parsimoniously explained by GBA2 inhibition, not GCS inhibition.[6][7][8]

GBA2 (non-lysosomal glucosylcerebrosidase) is a cytoplasmic enzyme that degrades glucosylceramide at the outer leaflet of cell membranes. Its physiological role and substrate profile overlap partially with lysosomal GBA (the Gaucher enzyme) but it operates in a different compartment. **Loss-of-function mutations in GBA2 cause autosomal recessive cerebellar ataxia and hereditary spastic paraplegia in humans**, establishing that this enzyme is critical for normal neurological function.

Inhibiting GBA2 changes membrane glucosylceramide distribution in a way that may secondarily modify neuroinflammation, autophagy and sphingolipid signaling pathways. The paradox of rising brain GlcCer during miglustat treatment is explained precisely by this mechanism: GBA2 normally degrades GlcCer, so inhibiting it raises GlcCer, the opposite of what GCS inhibition would do, and exactly what was observed.

Sinbaglustat, a brain-penetrant GBA2-preferring inhibitor which also inhibits GCS with lower potency, provides important mechanistic confirmation: in GM1 mouse models it ameliorated disease pathology and behavioral deficits *without affecting CNS ganglioside levels*, strongly supporting GBA2 as the functional

target rather than GCS.[17] Sinbaglustat was not advanced into clinical development by its originating company and has been shelved. Its value is as mechanistic validation of the GBA2 hypothesis, not as a clinical candidate.

VENGLUSTAT: THE AMETHIST TRIAL, GM1 BASKET DATA AND MECHANISTIC CONTEXT

Venglustat (GZ/SAR402671; Sanofi/Genzyme) is a brain-penetrant, selective GCS inhibitor. Unlike miglustat, it achieves measurable cerebrospinal fluid exposure and pharmacodynamic activity in the CNS, with negligible GBA2 inhibition at therapeutic doses. The AMETHIST trial (NCT04221451; Phase 3) enrolled patients in two arms: a randomized, double-blind, placebo-controlled study in late-onset GM2 gangliosidosis (N=59 in the RCT), and an open-label basket cohort that included 7 GM1 patients treated for up to 104 weeks.[10]

GM1 basket arm, primary data (N=7, open-label, 104 weeks):[10]

- CSF GM1 ganglioside: 29.1% median reduction from baseline at week 104
- CSF glucosylceramide: 70.2% median reduction, confirming target engagement at the GCS level
- FARS-neuro scores: decreased (improved) in GM1 participants over the study period
- 9-HPT completion times: decreased (improved)
- 25-Foot Walk Test: relatively stable
- Quality of life assessments: stable

One late-infantile GM1 participant, enrolled at age 2, died before week 104 from disease progression unrelated to study drug.[10] As an open-label single-arm cohort without a control group, these data are descriptive only: individual trajectories in a rapidly progressive disease, not controlled evidence of drug efficacy. They establish proof of concept for CNS target engagement in GM1 and provide the pharmacodynamic rationale for further clinical investigation.

Mechanistic context: the GM2 RCT. The randomized GM2 arm (N=59, placebo-controlled) provides the interpretive counterpoint. CSF GM2 fell by 47.6% in venglustat-treated patients versus 11.3% in placebo ($p<0.0001$), confirming that selective GCS inhibition can achieve substantial CNS ganglioside reduction. Yet the primary clinical endpoint, 9-HPT hand motor function, showed no significant difference from placebo ($p=0.74$). Secondary endpoints were likewise uninformative.[10] Biomarker success; clinical futility. This dissociation is precisely what the GBA2 hypothesis predicts: GCS inhibition alone, even when it meaningfully reduces substrate, does not engage the pharmacologically relevant pathway that drives clinical benefit.

What this means for patients. Any benefit miglustat might provide in GM1 is not from reducing ganglioside accumulation. It is instead from off-target modulation of membrane sphingolipid metabolism via GBA2. This is both an argument that the drug might still have some effect, through an unexpected mechanism, and an argument that a better-designed drug engaging GBA2 with adequate brain penetrance could provide meaningful benefit with less toxicity.

Part IV: Safety Profile, What the Data Show on Harm

4.1 GI TOXICITY (NEAR-UNIVERSAL)

Miglustat is a highly effective inhibitor of intestinal disaccharidases (sucrase, maltase, isomaltase) at concentrations far below those that affect GCS.[8] This causes predictable, dose-related GI toxicity. The figures below are from the Gaucher disease clinical trials reported in the US prescribing information, which is the largest and best-characterised safety dataset for this drug.[1]

- **Diarrhea:** reported in **89 to 100%** of patients[1]
- **Weight loss:** reported in **39 to 67%** of patients. In pediatric patients, concerns about growth and nutritional adequacy are substantial[1]
- **Tremor:** reported in **11 to 17%** of patients[1]
- **Interventions:** tremor and diarrhea are the adverse reactions most commonly requiring intervention, including dose reduction[1]

> **A figure this report no longer carries.** Version 1 referred to a high proportion of Gaucher patients discontinuing miglustat, and an earlier version of the companion family guide put that figure at approximately 85%. **No published source for any specific discontinuation percentage could be located**, and the US label reports no aggregate discontinuation rate. Clinical experience that patients frequently come off miglustat because of GI intolerance is widely reported and is consistent with the incidence figures above, but until a citable figure is found this report gives none. Eliglustat, a more selective GCS inhibitor that does not cross the blood-brain barrier, is the usual comparator in this discussion; the selectivity difference is documented[8], the comparative tolerability figures are not sourced here.

4.2 NEUROLOGICAL TOXICITY

This is the most concerning safety signal for patients with CNS disease.

- **Peripheral neuropathy:** documented in some long-term miglustat users; mechanism unclear but potentially related to GBA2 inhibition in the peripheral nervous system[1]
- **Cerebellar and coordination effects:** multiple cases of worsened coordination or new cerebellar signs in NPC patients on miglustat. Distinguishing this from disease progression is difficult but it has been noted
- **GBA2 loss-of-function phenotype risk:** because miglustat inhibits GBA2 at therapeutic concentrations, chronic dosing may pharmacologically phenocopy GBA2 loss-of-function mutations.[8] Human GBA2 mutations cause hereditary spastic paraplegia and cerebellar ataxia. This is a theoretical but mechanistically grounded risk for patients on long-term miglustat, especially those with neurological disease where baseline motor function is already compromised

4.3 COGNITIVE EFFECTS

Some caregivers and clinicians have reported subtle cognitive changes on miglustat. This is difficult to interpret in GM1 patients, where cognitive decline is part of the natural history, but the concern is registered in the literature.

4.4 DRUG INTERACTIONS

Miglustat is excreted predominantly renally. It does not significantly interact with most co-medications at the pharmacokinetic level, though additive GI effects with other agents are possible.[1]

Part V: Synthesis, What We Can and Cannot Conclude

WHAT IS WELL-ESTABLISHED

1. Miglustat's primary pharmacological target at therapeutic concentrations is **GBA2, not GCS**. This is supported by in vitro potency data (roughly 60-fold selectivity differential), by animal models showing brain GlcCer paradoxically rising during treatment, and by the functional replication of its effects by selective GBA2 inhibitors.[8][6][7][17]

2. Miglustat has demonstrated benefit in NPC in a randomized controlled trial.[3] The evidence base here is the best available for any neurological LSD indication of miglustat. This evidence is for neurological *stabilization*, not cure or reversal.

3. **There are no randomized controlled trials of miglustat in GM1 gangliosidosis.** None have been completed. Existing evidence consists of uncontrolled case series and retrospective cohorts.[5]

4. The preclinical GM1 evidence is weak. The primary mouse study showed biochemical effects but not survival extension, was confounded by caloric restriction, and is methodologically insufficient to conclude disease modification.[9]

5. Miglustat has a substantial toxicity burden. GI side effects are near-universal at standard doses.[1] Neurological risks via GBA2 inhibition are mechanistically plausible and potentially meaningful in a patient with underlying neurological disease.[8]

WHAT IS UNCERTAIN

1. Whether miglustat provides any disease-modifying benefit in GM1 type 2 patients. The clinical series cannot be dismissed outright: they document real patients who appeared to have a more favorable course than historical expectation.[5] But they cannot establish causality. GM1 type 2 has natural variability in course, and selection and ascertainment bias in case series is substantial.

2. Whether the GBA2 inhibition mechanism, even if real, is beneficial or harmful in the context of an ongoing neurodegenerative process. GBA2 inhibition changes membrane lipid composition in ways that may acutely reduce neuroinflammation (beneficial) but may also chronically impair neuronal membrane function (harmful). Long-term implications of sustained GBA2 inhibition in a patient with neurological disease are nascent.

3. The relevance of the Syner-G combination. The ketogenic diet component may provide the majority, or all, of any clinical benefit observed in Syner-G patients, with miglustat adding primarily GI toxicity.

THE VERDICT AS OF AUGUST 2026

Miglustat is **not supported by rigorous evidence as a disease-modifying treatment for GM1 gangliosidosis**. The preclinical rationale is undermined by pharmacological evidence that its CNS mechanism is off-target, GBA2 rather than GCS. The animal data are confounded and do not show survival benefit. Clinical evidence in GM1 specifically consists of low-quality observational series. Its toxicity profile is real and clinically significant.

This does not mean that every patient who used miglustat derived zero benefit. Natural history variability, placebo effects, caregiver effects and off-target biology make that impossible to rule out in individuals. But it does mean that miglustat cannot be recommended as a well-evidenced treatment for GM1, and that **the decision to discontinue it is scientifically defensible and fully consistent with the current state of knowledge**.

One boundary on that statement, stated explicitly because families act on it: no study has followed what happens to patients with GM1 when miglustat is withdrawn. The position above is a reading of the balance of evidence for benefit against the documented harm, not a finding from a discontinuation study, because no such study exists.

Part VI: What This Means Looking Forward

The finding that GBA2 inhibition, not GCS inhibition, drives the neurological effects of miglustat is, paradoxically, potentially good news for GM1 patients. It means:

- More selective, better-tolerated GBA2-engaging agents are in active clinical development for GM1. Sinbaglustat confirmed the GBA2 hypothesis in GM1 mice but was shelved by its originating company.[17] The clinical translation has instead been taken forward by nizubaglustat (Azafaros), now in a Phase 3 pivotal trial that includes GM1 patients[15]
- The therapeutic hypothesis is not dead, it has simply been revised. The question is no longer “can we slow ganglioside synthesis?” but “can we modify membrane sphingolipid homeostasis and neuroinflammation through GBA2?”
- The broader treatment landscape in GM1 is advancing on multiple fronts: symptomatic management, investigation of enzyme replacement therapy delivered intracerebroventricularly, and gene therapy approaches aimed at enzymatic correction. These reflect the direction the field is actually moving, not toward improving a failed SRT paradigm, but toward addressing the root cause

NIZUBAGLUSTAT: THE MECHANISTIC HYPOTHESIS TRANSLATED TO THE CLINIC

Nizubaglustat (AZ-3102; Azafaros B.V., Leiden, Netherlands), a dual inhibitor of both GCS and GBA2, was specifically engineered to overcome the lack of enzyme selectivity that causes miglustat’s GI side effects, to increase potency so as to significantly reduce the dose, to inhibit both GCS and NLGase with high and relatively equal potency, and to achieve high CNS penetration.

A Phase 1 first-in-human study in healthy adults documented measurable nizubaglustat concentrations in cerebrospinal fluid at multiple dose levels, directly confirming brain penetrance and resolving the principal pharmacological limitation of miglustat.[11] Preclinical studies in Sandhoff disease (GM2) mice demonstrated extended survival of roughly 22%, reduced CNS neuroinflammation (downregulation of GFAP, Itgax and Trem2), and behavioral improvements.[12]

Azafaros states that nizubaglustat is the only drug in development showing neurologic improvement in all three ganglioside storage disease preclinical models, GM1, GM2 and Niemann-Pick type C.[13] **The GM1 preclinical data behind that statement have not appeared as a standalone publication**, so the claim rests on the company’s account rather than on a peer-reviewed report.

Clinical status as of August 14, 2026.

- **Phase 3 (NAVIGATE; NCT07082543):** an 18-month randomized, double-blind, placebo-controlled trial in late-infantile and juvenile forms of GM1 and GM2 gangliosidosis, in patients aged 4 years and older. **Enrollment is closed at 75 participants and the study is active, not recruiting.** The primary endpoint is ataxia measured by the total and functional SARA scores from baseline to month 18. Primary completion is estimated for February 2028[15][16]
- **Phase 3 in NPC (NCT07082725):** a separate, simultaneous trial evaluates nizubaglustat in Niemann-Pick type C. GM1 patients are not eligible for this study
- **Phase 2 (RAINBOW; NCT05758922):** a randomized, double-blind, placebo-controlled 12-week study with long-term extension in 13 patients with GM2 gangliosidosis or NPC. **Completed May 2026.** Topline safety was reported in February 2026 at the WORLD Symposium, and the full results, covering pharmacokinetics and pharmacodynamics at 3 months and clinical and safety outcomes through 18 months, are now published[14][18]

- **Regulatory:** FDA has granted Rare Pediatric Disease designation, Orphan Drug designation and Fast Track status across GM1, GM2 and NPC; EMA has granted Orphan Medicinal Product designation and the MHRA an Innovation Passport[16]

Nizubaglustat does not represent a refinement of miglustat. It represents a systematic redesign informed directly by the mechanistic understanding detailed in this report: brain penetrance is necessary and achievable, and GBA2 engagement is the clinically relevant target.

References

Entries 1 to 17 are numbered identically in the companion Family Resource Series guide and on the Miglustat page at curegm1.org, so a given number refers to the same source in all three. Entry 18 appears in this report only.

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This report was prepared as a research synthesis and does not constitute medical advice. All treatment decisions should be made in consultation with the patient's clinical care team.

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