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/cell) models, clinical series, and expert commentary through early 2026

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, if one could partially block the upstream enzyme that makes that substrate, this could reduce the accumulation burden.

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

Miglustat has been **FDA-approved for Gaucher disease type 1** (2003) and **EMA-approved for Niemann-Pick type C (NPC)** neurological manifestations (2009) in adults and children for whom enzyme replacement therapy is not suitable. 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 MAY NOT REACH SUSTAINED THERAPEUTIC CONCENTRATIONS IN THE BRAIN

A core pharmacological objection to miglustat in GM1 is concentration-dependent: the blood-brain barrier does not substantially block CNS penetration of miglustat per se – cerebrospinal fluid concentrations have been measured at 31.4–67.2% of simultaneous plasma levels (Zavesca Prescribing Information; EMEA/CHMP/639529/2008 EMA Assessment Report). The more 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. 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*$^{-/-}$) mouse model [*PLoS ONE* 6(6):e21758]:
- Miglustat (NB-DNJ) improved motor performance, reduced neuroinflammation, and extended lifespan by ~34–41%
- **However:** Brain glucosylceramide (GlcCer, also known as GL1) increased more than *20-fold* in treated animals
- Brain GM2 (the substrate that accumulates in Sandhoff) was not meaningfully reduced
- A second-generation GCS inhibitor (Genz-529468) with better CNS penetration replicated the survival benefit but also paradoxically increased brain GlcCer.
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- **Conclusion of the authors:** The observed CNS benefit is inconsistent with GCS inhibition as the mechanism; "the most likely explanation is inhibition of GBA2". GBA2 is the gene that 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 review we will keep with the older terminology and use GBA2 when we speak of the enzyme. This enzyme has most of its effects in the brain where it converts GlcCer to ceramide (Cer). Inhibition of GBA2 (NLGase) increases GlcCer in the brain.

Nietupski et al. (2012), Niemann-Pick C (*NPC1*$^{-/-}$) mouse model [*Mol Genet Metab* 105(4):621–628]:
- Miglustat improved motor function, reduced CNS inflammation, and extended survival ~30–40%
- Brain GlcCer increased approximately **3-fold** in treated mice, exactly the opposite of what GCS inhibition would produce
- Liver GlcCer fell as expected (confirming peripheral GCS inhibition was occurring), while brain GlcCer rose
- CD68+ macrophage infiltration in the liver was unchanged despite substrate reduction there
- **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"

Shayman & Larsen (2014) review [*J Lipid Res* 55(7):1215–1225]:
- Comprehensive survey of small molecule SRT inhibitors for lysosomal storage diseases
- On miglustat's selectivity profile: miglustat inhibits GBA2 (non-lysosomal glucosylcerebrosidase) at concentrations **~60-fold lower** than those required to inhibit GCS
- At typical plasma concentrations in treated patients, GBA2 inhibition is the dominant pharmacological effect
- Additional off-target enzymes inhibited at clinically relevant concentrations include: intestinal disaccharidases (sucrase, maltase, isomaltase), glycogen debranching enzyme, and lysosomal GBA (acid β-glucosidase)

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 [Elliot-Smith et al., 2008, *Mol Genet Metab*]. These studies documented biochemical improvements and behavioral preservation in treated animals.

A methodological objection that substantially undermines interpretation of these results:

- Miglustat causes significant **gastrointestinal toxicity** (diarrhea, cramping, nausea, weight loss)

via disaccharidase inhibition in the gut

- 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 cited by proponents of miglustat in GM1 were not pair-fed, control animals ate ad libitum while treated animals were effectively on a caloric-restricted diet
- Caloric intake was never formally measured or reported
- 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$^{-/-}$ mice treated with NB-DNJ from birth:

- 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. The authors attribute this partly to severe rectal prolapse from GI toxicity
- The study endpoints at 15 weeks captured early-course animals; the behavioral benefit did not persist to later timepoints
- This is a profound contrast to the Sandhoff and NPC models, where survival extension was observed

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 (2014) make a theoretical point that applies directly to infantile and severe GM1: substrate reduction therapy is physiologically designed for conditions of *partial* enzyme deficiency, where residual enzyme activity can clear substrate when production is reduced. For conditions with **near-complete or complete enzyme loss** (as in infantile GM1 with pathogenic variants) reducing substrate synthesis rate does not help because there is essentially no enzymatic clearance to augment. The substrate will accumulate regardless. Juvenile-onset (type 2) patients with at least some residual enzyme activity, as evidenced by their later presentation compared to infantile forms, are in a theoretically different category, but 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) [*Lancet Neurol* 6(9):765–772], randomized controlled trial (n=29):

- Patients with NPC (12 years, ambulatory) randomized to miglustat vs. 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, cognition, stabilization in treated vs. decline in controls

- Interpretation: meaningful neurological stabilization over 12 months

A non-controlled open-label extension of the original trial (Wraith et al. 2010) reported continued neurological stabilization in adult and juvenile NPC patients over 24 months of miglustat therapy. Consensus clinical management guidelines (Geberhiwot et al. 2018) synthesizing multicenter European registry experience, likewise support neurological stabilization as the primary documented benefit in appropriately selected NPC patients.

Key caveat: The mechanism of benefit in NPC is also not fully understood and the underlying pathophysiology is very different from GM1. In NPC, there is a defect in a transporter, while in GM1 the defect 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. 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) [*Mol Genet Genomic Med* 8:e1371], multicenter Italian cohort, pediatric GM1 type 2 patients:

- 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 sizes; comparison to historical controls with inherent selection bias

- Outcome assessment: largely qualitative clinician impressions and parent/caregiver reports
- **Limitations acknowledged by authors:** No randomization, no blinding, substantial heterogeneity in dose/duration/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/retrospective design.

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

Formal clinical trials of miglustat in GM2 gangliosidosis (Tay-Sachs, Sandhoff) were conducted in the early 2000s. These yielded **limited success**, some patients with later-onset disease appeared to stabilize; 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 with the rationale that ketosis independently alters neuronal metabolism and may have neuroprotective effects that are 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 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/ascertainment effects

Part III: Mechanism Revisited, What GBA2 Inhibition Actually Means

The preclinical studies (Ashe 2011, Nietupski 2012, Shayman & Larsen 2014) 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.

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 (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 (Wannemacher et al., 2025), a brain-penetrant GBA2-preferring inhibitor (which also inhibits GCS with lower potency), provides important mechanistic confirmation: in GM1 mouse models, sinbaglustat ameliorated disease pathology and behavioral deficits without affecting CNS ganglioside levels, strongly supporting GBA2 as the functional target rather than GCS. 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 (Tifft et al. 2026).

GM1 Basket Arm — Primary Data (N=7, Open-Label, 104 Weeks)

For the seven GM1 patients in the basket cohort, the AMETHIST investigators reported:

- **CSF GM1 ganglioside: 29.1%** (median reduction from baseline at week 104)
- **CSF glucosylceramide: 70.2%** (median), 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 (25-FWT):** 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. 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. Biomarker success; clinical futility. This dissociation—biochemistry working, function unchanged—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 — such as nizubaglustat, currently in Phase 3 — 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. This causes predictable, dose-related GI toxicity:

- **Diarrhea, bloating, cramping**: reported in >70% of patients in clinical trials
- **Weight loss**: clinically significant in many patients; in pediatric patients, concerns about growth and nutritional adequacy are substantial
- **Discontinuation rate in Gaucher disease:** a high proportion of Gaucher patients on miglustat in clinical practice eventually discontinue, primarily due to GI intolerance, compared with a substantially lower discontinuation rate on

eliglustat, a more selective GCS inhibitor that does not cross the blood-brain barrier

- The difference in tolerability directly reflects miglustat's non-selectivity

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

- **Cerebellar/coordination effects**: multiple cases of worsened coordination or new cerebellar signs in NPC patients on miglustat, distinguishing this from disease progression is difficult but 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. Human GBA2 mutations cause HSP 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 metabolized and 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.

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 (~60× selectivity differential), by animal models showing brain GlcCer paradoxically rising during treatment, and by the functional replication of its effects by selective GBA2 inhibitors.
2. **Miglustat has demonstrated benefit in NPC in a randomized controlled trial.** 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.
4. **The preclinical GM1 evidence is weak.** The primary mouse study (Elliot-Smith 2008) showed biochemical effects but not survival extension, was confounded by caloric restriction, and is methodologically insufficient to conclude disease modification.
5. **Miglustat has a substantial toxicity burden.** GI side effects are near-universal at standard doses and have caused a high rate of long-term discontinuation in Gaucher disease. Neurological risks via GBA2 inhibition are mechanistically plausible and potentially meaningful in a patient with underlying neurological disease.

WHAT IS UNCERTAIN:

1. **Whether miglustat provides any disease-modifying benefit in GM1 type 2 patients.** The clinical series (Fischetto 2020 and others) cannot be dismissed outright, they document real

patients who appeared to have a more favorable course than historical expectation, but they cannot establish causality. GM1 type 2 (juvenile-onset) 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. At the WORLD Symposium in 2026, Azafaros presented 18-month data in which, of participants assessed, 45% showed improvement or stabilization of ataxic signs.
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 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, not GCS), the animal data are confounded and do not show survival benefit, and 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.

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:

1. **More selective, better-tolerated GBA2-engaging agents are in active clinical development for GM1.** Sinbaglustat (2025) confirmed the GBA2 hypothesis in GM1 mice but was shelved by its originating company and was not advanced into clinical trials. The clinical translation has instead been taken forward by **nizubaglustat** (Azafaros), now in a Phase 3 pivotal trial that includes GM1 patients — detailed below.
2. **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 AMETHIST data: GM1 basket arm and mechanistic lessons. The 2026 AMETHIST trial publication (Tifft et al. 2026) provides two complementary insights. In the GM1 open-label basket cohort (N=7, 104 weeks), venglustat produced a median **29.1% reduction in CSF GM1 ganglioside** and **70.2% reduction in CSF glucosylceramide**, with FARS-neuro and 9-HPT scores showing improvement signals. These are descriptive data without a control arm, but they establish that a selective GCS
inhibitor can achieve pharmacodynamically meaningful target engagement in GM1 CNS—proof of concept for brain penetrance and substrate reduction in this disease. The mechanistic counterweight comes from the GM2 RCT arm: a 47.6% reduction in CSF GM2 (vs. 11.3% placebo)

produced no clinical benefit (p=0.74 on 9-HPT). That dissociation—biomarker success, clinical futility— is compelling evidence that GCS inhibition alone does not engage the therapeutically relevant pathway in gangliosidoses. The relevant target, as this report details, is GBA2, not GCS per se.

1. **The broader treatment landscape** in GM1 is advancing on multiple fronts: symptomatic management (seizure control, motor support), 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. The work described above has directly informed a next-generation clinical program. **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 which causes the GI side-effects, to increase potency to significantly decrease the dose, to make a balanced inhibitor to inhibit both GCS and NLGase with high and relatively equal potency, while having 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 (Paquet Luzy et al. 2024). Preclinical studies in Sandhoff disease (GM2) mice demonstrated extended survival (~22%), reduced CNS neuroinflammation (downregulation of *GFAP, Itgax, and Trem2*), and behavioral improvements (Landskroner et al. 2026). Azafaros reports that nizubaglustat is the only investigational compound showing neurologic benefit in all three ganglioside storage diseases (GM1, GM2, and Niemann-Pick type C) across preclinical models, which implies GM1 efficacy data exist, though these have not yet appeared as standalone publications.

Clinically, nizubaglustat has advanced to Phase 3. NCT07082543 is a pivotal 18-month randomized, double-blind, placebo-controlled trial enrolling patients with GM1 and GM2 gangliosidoses, aged 4 years and older; a separate, simultaneous Phase 3 trial (NCT07082725) evaluates nizubaglustat in Niemann-Pick type C disease. The primary endpoint is ataxia measured by the SARA

scale, with sites including UCSF Benioff Children's Hospital Oakland, Mayo Clinic in Rochester, and the Lysosomal Rare Disorders Research and Treatment Center (LDRTC) in Fairfax, VA. A preceding Phase 2 double-blind study (RAINBOW; NCT05758922) enrolled 13 patients with GM2 and NPC and reported positive safety topline results in February 2026 at the WORLD Symposium.

FDA has granted Rare Pediatric Disease designation, Orphan Drug designation, and Fast Track status across all three indications; EMA has granted Orphan Designation for GM1 and GM2. 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.

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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.