Rare Diseases Clinical Research Network

Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)

Lysosomal Disease Network

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Protocol Synopsis

Protocol Number:	LDN 6729
Protocol Title:	Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)
Study Chair:	Jeanine R. Jarnes, PharmD
Statistician:	Kyle D. Rudser, Ph.D.
Consortium:	Lysosomal Disease Network
Participating Sites:	University of Minnesota
Activation Date:	02/24/2016
Sample Size:	A total of 30 infants or children: • 5 patients with infantile Tay-Sachs disease • 5 patients with juvenile Tay-Sachs disease • 5 patients with infantile Sandhoff disease • 5 patients with juvenile Sandhoff disease • 5 patients with infantile GM1 gangliosidosis • 5 patients with juvenile GM1 gangliosidosis
Target Enrollment Period:	Rolling enrollment of patients with infantile or juvenile gangliosidosis over the next five years; whenever possible, making one yearly visit to the University of Minnesota
Study Design:	Interventional study
Therapeutic Agent:	Miglustat
FDA IND Status:	IND 127636 Active
Phase:	Phase II
Methodology:	Combination enteral therapy
Study Design:	Single arm, open-label treatment study
Study Duration:	5 Years
Primary Study Objective:	To assess the impact of Syner-G therapy on overall survival in patients with infantile and juvenile forms of gangliosidosis
Secondary Study Objective:	To evaluate effects of Syner-G therapy in pediatric gangliosidoses patients on their neuro-developmental status
Study Population and Main Eligibility/Exclusion Criteria:	Study Population: Any infant or juvenile patient with a gangliosidosis disease. Inclusion Criteria: 1.) Subjects must have a documented infantile or juvenile gangliosidosis disease. 2.) Age: 17 years or less at time of enrollment. 3.) Subjects and their caregivers must work closely with their University of Minnesota ketogenic diet team, and with their local ketogenic diet team, which must include a ketogenic dietician and a neurologist trained in the ketogenic diet. Exclusion Criteria: 1.) A desire to not participate. 2.) Children with severe renal impairment will not be enrolled in this study. 3.) Post-pubertal females who are pregnant, or who are unwilling to use highly-effective methods to prevent pregnancy, will be excluded from this study. 4.) Breast-feeding females will be excluded from this study. 5.) Subjects who have an allergy to miglustat or any of the

	components within the drug product will be excluded from this study.
Primary Outcome Measures:	Retrospective and prospective data will be collected, that include: Overall participant survival, evaluated based on chronological age at time of death or at conclusion of study, whichever occurs first.
Secondary Outcome Measures:	Retrospective and prospective data will be collected, that include: The rate of change (i.e., slope) in neurocognitive functioning over the duration of follow-up will be determined; and will also be compared to available published natural history data. This analysis will be conducted separately for each of the two disease sub-types: infantile and juvenile. The primary neurocognitive measure for both pediatric groups is age-equivalent scores of the Bayley Scales of Infant and Toddler Development for expressive communication, receptive communication, fine motor skills and gross motor skills. The secondary neurocognitive measure for both pediatric groups is standard and age-equivalent scores of the Vineland Adaptive Behavior Scales for communication, daily living skills, socialization and motor skills, and the Vineland composite standard score.
Statistical Considerations (sample size and analysis plan):	The sample size (number of enrolled subjects) will be large enough to detect trends and differences. The primary analysis for Syner-G therapy will use the intention-to-treat (ITT) population and evaluate overall survival based on chronological patient age. Median survival will be compared to previously reported natural history studies of infantile and juvenile gangliosidoses. For rate of change in neurocognitive functioning over the duration of follow-up, using general estimating equations (GEE) and an exchangeable working correlation structure, variance estimation for confidence intervals and p-values will take into account the possible correlated nature of multiple measurements on the same individual. Supportive analyses will include evaluation using the per-protocol (PP) population. Subgroup analyses: analyses will be repeated separately among the infantile and juvenile forms of both GM1 and GM2 gangliosidosis.
Sponsors (federal, state, foundation and industry support):	National Institutes of Health (NIH)

1.0 Disease Overview

The gangliosidoses are fatal genetic conditions inherited in an autosomal recessive pattern. The GM2 gangliosidoses are caused by mutations to the genes that encode production of the lysosomal enzymes hexosaminidase A and hexosaminidase B, causing Tay-Sachs disease and Sandhoff disease, respectively. Without these enzymes individuals cannot catalyze the biodegradation of GM2 ganglioside.

The GM2 gangliosidoses disease have an estimated overall occurrence rate of 1:200,000 live births for Tay-Sachs disease, and 1:400,000 live births for Sandhoff disease.[1] The carrier rate for GM2 gangliosidosis diseases in the general population is estimated to be 1:250.[1,2] Among Ashkenazi Jews, French Canadians, and Louisiana Cajuns the incidence rate is much higher, with overall elevated incidence rates of 1 in 27 persons thought to be a genetic carrier for a GM2 gangliosidosis disease (Tay-Sachs disease and Sandhoff disease).[2]

Before the advent of population-based carrier screening, education, and counseling programs for the prevention of Tay-Sachs disease in Jewish communities, the incidence of Tay-Sachs disease was about one in 3,600 Ashkenazi Jewish births. Currently, due to increased screening and awareness, the incidence of Tay-Sachs in Ashkenazi Jews of North America has been reduced by greater than 90%.[1,3] Although the incidence of Tay-Sachs disease has significantly declined in the Jewish community, the disease has been reported in children of virtually all ethnic, racial and religious groups. Irish Americans have a 1 in 50 chance of a person being a carrier. Sandhoff disease, unlike Tay-Sachs, occurs more commonly in non-Jewish populations.[1,4]

GM1 gangliosidosis is caused by mutations to the gene that encodes β-galactosidase, leading to deficiency of β-galactosidase. Without the β-galactosidase enzyme to break it down, ganglioside accumulates in neuronal cells and other tissues, leading to mental and physical deterioration. The worldwide prevalence of GM1 gangliosidosis is estimated to be 1:100,000 to 200,000 live births.[1] In Malta and Brazil, and in the Roma and Cypriot populations, a high prevalence of GM1 gangliosidosis has been found.[5]

The GM1 and GM2 gangliosidoses are comprised of three major types, differentiated by age of onset of symptoms: infantile (Type I), late-infantile/juvenile (Type II), and late-onset, in which symptom onset occurs in adulthood (Type III). The infantile form of the disease is the most aggressive form and has a rapid neurological decline with death early in childhood. The juvenile forms involve a later-childhood onset of symptoms, with a slower neurological decline compared to the infantile forms, and usually result in death during adolescence. The late-onset forms of gangliosidoses have a later symptom onset, with first symptom often being noted while the patients are in their twenties and thirties. Late-onset forms are characterized by poor motor coordination and progressive weakness. Some patients develop psychotic behaviors. Patients with late-onset forms of gangliosidoses also have decreased life expectancy, albeit to a significantly lesser degree than those with either infantile or juvenile forms.[6]

1.1 Description of the infantile and juvenile forms. The classical infantile forms of these diseases can be described as having rapidly progressive neurologic deterioration with death often occurring by age three to four years old; whereas death usually occurs in later childhood in the juvenile form.[7-9]

The following neurologic signs occur approximately in the sequence listed below:

- Progressive hypotonia and motor weakness
- Poor head control
- Failure to turn over, crawl, or sit
- Eventually becoming hypertonic with exaggerated reflexes
- Decreasing eye contact and focusing
- Interacts very little with the environment, eventually becoming unresponsive to exogenous stimuli and reaching vegetative state
- Hyperacusis initially evidenced by an exaggerated startle response to sharp sounds, eventually becoming unresponsive and inattentive.
- Seizures commonly begin after first year of life and vary in type and frequency
- Macrocephaly commonly develops by 1 ½ to 2 years of age due to reactive cerebral gliosis
- Ocular development of cherry-red macular spots
- Progressive visual inattention with blindness by the second year of life.

1.1.2 Neuroimaging in the infantile/juvenile forms. In the infantile forms of gangliosidoses, brain MRIs are characterized by abnormalities in the basal ganglia and thalamus, spreading later to the rest of the brain with atrophic changes. Specific gross neuropathological characteristics of the phases of gangliosidoses are: in 0-14 months of illness, changes are described as moderate atrophy with slight decrease in brain weight, narrowing of cerebral sulci and mild ventricular dilatation; in 15-24 months of illness there is normal or mildly increased brain weight and volume, and disproportionate atrophy of cerebellum and brain stem; once illness reaches 24 months of duration there is significant cerebral expansion with broadened and flattened surface convolutions, marked atrophy of cerebellum and brain stem, demyelinization, extensive edema, and cystic degeneration of cerebral white matter.[8-10]

In a natural history study of 155 patients with juvenile GM2 gangliosidosis by Maegawa et al.[11], (96 with Tay-Sachs disease, 33 with Sandhoff disease, 2 with the AB variant, and 9 patients that were uncharacterized), 35 of the patients had brain imaging studies. The most common brain-imaging finding was cerebellar atrophy and the second most common finding was cerebral atrophy, although cerebral atrophy and white matter changes appeared to precede cerebellar atrophy.[11]

1.1.3 Neurodevelopmental functioning in infantile and juvenile gangliosidoses. Available natural history data for the infantile and juvenile gangliosidoses are limited. Natural history studies of infantile and juvenile GM2 gangliosidoses by Bley et al.[9], Maegawa et al.[11] and Smith et al.[12] are based on surveys of child neurodevelopment. These studies show predictable downward trajectory consistent with childhood dementia and catastrophic neuro-degenerative processes, ultimately resulting in death during childhood.[9,11,12]

A survey based study of 316 patients with infantile GM2 gangliosidosis (survey-based data from 92 patients, data from 103 patients in the National Tay-Sachs and Allied Diseases patient advocacy group's database, and 121 patients reported in the literature), it was noted that in infantile GM2 gangliosidosis, the most common onset symptoms were developmental delay, startle-response and hypotonia.[9] Among the 92 patients surveyed, there were few differences noted in phenotype between infantile Tay-Sachs disease and infantile Sandhoff disease, although a tendency was observed for visual problems, seizures and movement abnormalities to occur earlier in the patients with Tay-Sachs disease.[9] As the disease advanced, seizure management often became the primary focus of clinical care.[9]

In the study by Maegawa et al. the mean onset of symptoms in juvenile GM2 gangliosidoses was reported as 5.3 ± 4.1 years, with gait disturbances, incoordination, speech difficulties and developmental delay being the most common symptoms noted at onset.[11] Neuropathy and psychiatric disturbances were found to be more common in patients with juvenile Sandhoff disease compared to juvenile Tay-Sachs disease.[11] In patients with juvenile Sandhoff disease, sleep problems, diarrhea and constipation were observed to be more common than in the patients with juvenile Tay-Sachs disease.[11] Dysphagia, sphincter incontinence and sleep problems were more common at the time of symptom onset in Tay-Sachs disease.[11] But this study found no other statistically significant differences between the patients with juvenile Tay-Sachs disease compared to patients with juvenile Sandhoff disease.[11]

1.1.4 Natural history survival data in infantile and juvenile gangliosidoses. The study by Bley et al. showed the median age of death in the infantile form was 47 months.[9] The case histories of 155 patients with juvenile GM2 gangliosidosis that were reviewed by Maegawa et al. were found to have a median survival of 14.5 years.[11] Nearly half of the patients died within the first decade of life, and roughly 25% of the patients lived into their late teens.[11] No statistically significant differences were found between the patients with Tay-Sachs disease and those with Sandhoff disease.[11]

2.0 Description of Late-onset or Type III Forms of Gangliosidosis Diseases

Late-onset hexosaminidase A deficiency (a.k.a. LOTS, the acronym for Late-Onset Tay-Sachs) and late-onset GM1 gangliosidosis represent a more slowly progressing neurodegeneration, associated with low levels of residual Hex A enzyme activity or *β*-galactosidase enzyme activity, respectively. Early symptoms may range from muscle weakness to extrapyramidal findings to altered cerebellar manifestations.

The age of onset in LOTS ranges from early childhood to the end of the second decade. In the adult-onset forms of gangliosidosis, CNS involvement is widespread with some neurologic findings predominant. In some individuals, extrapyramidal signs of dystonia and choreoathetosis may be evident.[13,14] In others, cerebellar signs of dysarthria, ataxia, lack of coordination, and abnormalities of posture develop between two and twenty years of age; however, cognitive and verbal skills tend to be involved later in the course.[13,14] Some individuals with adult-onset disease show progressive muscle wasting, weakness, and fasciculations[13], upper motor neuron signs, nonspecific cerebellar atrophy[7], and abnormalities of saccades.[13,14] Movement disorders such as dystonia and dyskinesia occur in almost 50% of all patients.[14]

Cognitive functioning is often noted to be normal in patients with late-onset forms of gangliosidoses.[15] For patients with late-onset Tay-Sachs disease in whom impaired cognitive status was documented, the severity of the impairment ranged from mild memory deficits to significant global cognitive decline.[15] As reported in the MacQueen et al. study of patients with late-onset Tay-Sachs disease, repeat testing at age 18 revealed persistent severe cognitive limitations in language, visuospatial abilities, psychomotor coordination, memory and executive functions.[15] More recent studies indicated cognitive dysfunction and dementia can be observed in some cases but is not universally present (Frey et al. 2005).[16] As many as 40% of individuals with late-onset Tay-Sachs disease have psychiatric manifestations (without dementia), including recurrent psychotic depression, bipolar symptoms and acute hebephrenic schizophrenia with disorganization of thought, agitation, delusions, hallucinations, and paranoia.[17] Impairment of executive functioning, visual spatial functions, and memory (retrieval) has also been observed.

These neuropsychological dysfunctions could be related to cerebellar abnormalities. Schmahmann and Sherman have hypothesized a cerebellar cognitive affective syndrome which has as its core difficulty a "dysmetria of thought", with flattened affect and lack of inhibition.[18]

2.1 Neuroimaging in late-onset gangliosidosis. The first description of neurologic and psychiatric findings in a large case series of late-onset Tay-Sachs disease reported involvement of upper and lower motor neurons, basal ganglia, and cerebellum, with sparing of sensory systems and cranial nerves.[14] In Frey's study, brain MRIs obtained in 86% of their patients revealed the uniform presence of marked cerebellar atrophy, regardless of disease stage.[16] Neuropsychological results in the same study indicated delayed verbal recall and problems with cognitive processing, visual sequencing, and set shifting; none of these patients had signs of significant global decline or dementia.[16]

3.0 The AB variant of GM2 Gangliosidosis

The AB variant of GM2 gangliosidosis is a rare form of GM2 gangliosidosis in which a genetic defect occurs in the gene that codes for the GM2 ganglioside activator protein (GM2A gene), rather than on the α-subunit (HEXA gene) or β-subunit (HEXB gene) of the β-hexosaminidase A. The GM2 ganglioside activator protein is a co-factor for β-hexosaminidase A enzyme and is required for activation of β-hexosaminidase A. Thus, in patients with the AB variant of GM2 gangliosidosis, β-hexosaminidase A enzyme is devoid of activity.[1,6]

4.0 The B1 Variant of GM2 Gangliosidosis

The B1 variant of GM2 gangliosidosis is a form of Tay-Sachs disease in which a genetic defect in α-subunit of β-hexosaminidase A causes in a defect in the catalytic region of the αβ-dimer of β-hexosaminidase A, resulting in inhibition of the activity of the catalytic region of the αβ-dimer of β-hexosaminidase A and inactivity towards the GM2 ganglioside substrate.[1,6,19]

5.0 Relevant Pre-Clinical Data

5.1 Pre-clinical pharmacokinetic studies of miglustat. A pharmacokinetic profile study of miglustat in healthy rats showed miglustat to be well absorbed after a single oral administration with an oral bioavailability of 40-60%.[20] Miglustat is eliminated renally by glomerular filtration and active secretion.[20] Hepatic clearance of miglustat was shown to be negligible.[20] Miglustat was found to have good partitioning into most tissues evaluated, including bone marrow, lungs, heart, kidney, bladder, liver, stomach, and small and large intestine.[20] Miglustat showed appreciable distribution into the rat brain tissue.[20] The ratio of tissue:plasma AUC for the rat brain was 0.40.[20] Miglustat elimination half-life in the rat plasma was approximately 5 hours, but was significantly longer in the brain tissue at 17 hours.[20]

A study of miglustat by Ashe et al. in a Sandhoff mouse model showed that miglustat therapy, dosed at 600 mg/kg/day, resulted in a greater that 10-fold higher levels of glucocerebroside in the brain, the clinical significance of which is not known.[21] Despite the increase in glucocerebroside, the Sandhoff mice treated with miglustat showed significant reduction of GM2 ganglioside in the brain, delayed loss of coordination and motor function, and significant extension of lifespan (increased by 41%).[21]

5.1.1 Studies of ketogenic diet combined with miglustat in the Sandhoff disease mouse. A study in adult Sandhoff disease mice in which mice were divided into 4 groups, one group

receiving a standard diet, one group receiving a standard diet and miglustat, one group receiving a restricted ketogenic diet, and one group receiving a restricted ketogenic diet and miglustat, showed the combination of a restricted ketogenic diet and miglustat resulted in a significant reduction of GM2 content in the forebrain and a 3.5-fold higher cortex miglustat brain content compared to mice receiving a standard diet and taking miglustat.[22] Pharmacokinetic studies in mice indicate that only about 25-40% of the miglustat dose reaches the brain tissue, thus the 3.5-fold higher cortex concentration of miglustat, when given in combination with a ketogenic diet, represents a possible mechanism of synergy for potentially achieving fully bioavailability of miglustat to the CNS.[22] Although no human studies of combination treatment with miglustat and ketogenic diet have been published, the ketogenic diet has demonstrated safety and efficacy for seizure management in children for many decades[28-30] and holds potential for enhancing CNS bioavailability of miglustat and improving clinical outcomes in patients with gangliosidoses.

6.0 Relevant Available Clinical Data in Gangliosidoses

Results of previous clinical trials for gangliosidoses. Currently there are no approved therapies to treat any of the gangliosidoses. Studies of monotherapy with pyrimethamine and monotherapy with miglustat for treatment of gangliosidoses have been done and have demonstrated safety, but have not demonstrated notable clinical improvement.

7.0 Clinical Trials of Miglustat for Gangliosidoses and Relevant Clinical Studies

Miglustat is a small molecule that has partial bioavailability to the CNS after oral administration, and which reduces production of a number of glycosphingolipids, including GM1 and GM2 gangliosides, through inhibition of glucosylceramide synthase in the glycosphingolipid pathway, and may be useful to decrease the pathological accumulation of GM1 and GM2 gangliosides.[7] Miglustat is approved in the United States, Europe, Canada, Switzerland, Turkey, Brazil, and Australia for treatment of adult Gaucher disease type I. Miglustat is approved in Europe, Canada, Switzerland, Turkey, Brazil, and Australia for treatment of Niemann-Pick disease type C.[7,26]

Studies of miglustat in infantile, juvenile and adult gangliosidoses have demonstrated safety, but do not show significant clinical improvement. [23-25] A study of miglustat therapy in two patients with infantile Tay-Sachs disease who were given miglustat for 12 months showed no adverse effects at a dose of 100 mg daily for 3 months (divided into 3 doses daily).[23] The dose was doubled, increased to 200 mg daily after 3 months (divided into 3 doses daily) and this resulted in diarrhea and weight loss.[23] Reducing the dose back to 100 mg daily resulted in resolution of the diarrhea and weight loss.[23] The patients were continued at this lower dose during the remainder of the 12 months of the study.[23] Notably, neither patient developed macrocephaly during the 12 months of treatment.[23] Concentrations of miglustat in the cerebrospinal fluid (CSF) versus plasma varied from 1.84% to 27.3% of the concentration in the plasma.[23] Although miglustat therapy was well tolerated at 100 mg daily, the patient's neurological symptoms continued to worsen and encephalic imaging studies showed worsening myelination patterns and brain atrophy.[23]

In a 3-month safety and pharmacokinetic study of 11 pediatric GM2 gangliosidosis patients (5 with infantile and with 2 juvenile Tay-Sachs disease, 1 with infantile Sandhoff disease and 3 with juvenile Sandhoff disease), miglustat was dosed at 30-200 mg 3 times daily.[24] Patients with a body surface area (BSA) less than 0.8 m^2 were given miglustat 50-90 mg 3 times daily.[24]

Patients with BSA 0.8-1.3 m^2 were given 100 mg 3 times daily, and patients with BSA greater than 1.3 m^2 were given 200 mg 3 times daily.[24] Miglustat was shown to be safe and tolerable drug, with the most common side effect being mild to moderate diarrhea which could be controlled by dietary modification.[24] The pharmacokinetics was found to not differ between the infantile and juvenile patients, and demonstrated a 2-compartmental model with terminal half-life of about 10 hours.[24] Miglustat did not accumulate to any appreciable exent.[24]

In a study of 30 adult patients with late-onset Tay-Sachs disease (age range 18-56 years), 20 patients were randomized to receive miglustat 200 mg 3 times daily; and 10 patients were randomized to receive no miglustat for 12 months; followed by an additional 24 months in which all the patients were allowed to receive miglustat.[25] Nineteen patients completed the 36 month study period (11 who were randomized to receive miglustat and 8 who were randomized to receive no miglustat during the first 12 months).[25] This study showed safety, but no measureable benefits over the initial 12 month period, as well as the 36 month period.[25] Studies of miglustat in infantile, juvenile and adult gangliosidoses have demonstrated safety, but do not show significant clinical improvement. [23-25]

8.0 Clinical Experience with Ketogenic Diet for Seizure Management

The ketogenic diet is a high-fat, low-carbohydrate diet that is an established and effective non-pharmacologic treatment for epilepsy in children.[28-30] A highly restricted Ketogenic diet, or 4:1 ketogenic diet, is often the form of the diet used for recalcitrant seizures and consists of 4 grams of fat to 1 gram of combination of protein and carbohydrate.[28-30]

For patients with seizures recalcitrant to standard regimens using anti-seizure medications, the ketogenic diet has been shown to be effective for seizure management in many patients.[27] In a meta-analysis of 1084 patients from 19 different centers, the ketogenic diet was shown to result in 16% of patients becoming seizure-free, 32% of patients experiencing a >90% reduction in seizures, and 56% of patients experiencing a >50% reduction in seizures.[27] The ketogenic diet should be implemented under close clinical care of a ketogenic diet team specially trained in the ketogenic diet, and minimally include: a ketogenic dietitian, neurologist and pharmacist.[28-30]

Although the ketogenic diet has not been studied clinically in gangliosidosis patients, a pre-clinical study (described above) in adult Sandhoff disease mice (adult β-hexosaminidase knockout mice) shows that the ketogenic diet may be promising for the gangliosidoses for: 1) minimizing or reducing severity of food-drug interactions of Zavesca®; 2) reducing seizure activity; and 3) increasing the bioavailability of miglustat to the central nervous system.[22]

The ketogenic diet has been safely used in children and adults for many decades.[28-30] Patients may experience constipation with use of the ketogenic diet, especially during the initiation phases of the ketogenic diet.[28-30] Patients should be monitored for hypoglycemia 2 to 3 times daily during the initiation of the ketogenic diet, more frequently during adjustments to the ketogenic diet, and then periodically after they are stabilized on the ketogenic diet, as deemed appropriate by the patient's clinical ketogenic diet team.[28-30] A rare side effect of the ketogenic diet is increased risk of kidney stone formation.[28-30] Ketogenic diets, when properly followed, have not shown adverse effects on lipid profiles, but due to the higher fat content of the ketogenic diet, plasma lipid profiles should be monitored regularly.[28-30] Some patients have experienced a transient increase in seizures during the initiation of the ketogenic diet.[28-30]

8.1 Clinical significance of this study. To date, combination therapy for the gangliosidoses has not been formally studied. Studies of monotherapy with miglustat for treatment of gangliosidoses have demonstrated safety, but have not demonstrated notable clinical improvement. This study will evaluate combination therapy for treatment of the gangliosidoses, using miglustat combined with a ketogenic diet, to learn if this combination therapy approach will improve overall survival and clinical outcomes compared to previous trials with miglustat alone.

9.0 Clinical Experience with Combination Therapy at the University of Minnesota

At the University of Minnesota, the combination therapy using miglustat and the ketogenic diet has been tried in seventeen children with gangliosidosis diseases in a clinical care setting. Of these seventeen patients, there are four patients with infantile GM1 gangliosidosis, five patients with juvenile GM1 gangliosidosis, four patients with infantile Tay-Sachs disease, two patients with juvenile Tay-Sachs disease and two patients with infantile Sandhoff disease. The miglustat dose was titrated, as tolerated for gastrointestinal side effects, to achieve goal dose of 300 mg daily.

All seventeen patients were put on a combination of ketogenic diet and miglustat. Duration on therapy, to date, ranges between 4 months and 4 years. Five of the seventeen patients have been on the combination regimen for between 3.5–4 years. All seventeen patients have tolerated the combination therapy well. Of note, one patient, a 3-year old male with late-infantile GM1 gangliosidosis, showed mild improvement in visual reception, receptive language and expressive language domains after his first 6 months of full dose miglustat and full ketogenic diet; however, persistent decline in fine and gross motor domains continued. After 4 months of treatment with goal dose miglustat, a 10-month old female with GM1 gangliosidosis showed stabilization in the cognitive, receptive and expressive communication domains. Fine and gross motor skills showed decline, but after 3 years on treatment have stabilized. Her adaptive skills showed a significant rebound after 4 months treatment, although they continue to not approach the normal baseline. This patient also experienced a reduction in seizure frequency and severity. A 2.5 year-old male with infantile Tay-Sachs disease has shown a stable pattern in the communication and motor domains with some decline in the cognitive domain and adaptive skill after 2 months of treatment with goal dose miglustat. Overall, the combination of miglustat with ketogenic diet has been very well tolerated in all the patients, with no notable toxicities. Neuropsychiatric evaluations have shown improvement in some domains for patients using the goal miglustat dose; seizure frequency and severity have improved in all the patients; and preliminary results suggest further improvement may be possible with the combination of miglustat and the ketogenic diet.

10.0 Investigational Agent: Miglustat

10.1 Miglustat description and mechanism of action. Miglustat is a competitive and reversible inhibitor of glucosylceramide synthase enzyme, which is the first enzyme that acts in a series of reactions in the glycosphingolipid pathway. Miglustat therefore reduces the biosynthesis of glycosphingolipid in the glycosphingolipid pathway, including the reduction of GM1 and GM2 ganglioside.[23-27] Miglustat's chemical name is 1,5-(butylimino)-1,5-dideoxy-D-glucitol. The chemical structure is $C_{10}H_{21}NO_4$. Miglustat has a molecular weight of 219.28. Miglustat is available as a crystalline solid that is highly water soluble. Miglustat is commercially available under brand name Zavesca®, in 100 mg capsules.[26]

10.2 Miglustat indications. Miglustat is FDA approved for treatment of Gaucher disease type I, in patients for whom intravenous enzyme replacement therapy is not an option. Miglustat is approved in the European Union for the treatment of pediatric patients with Niemann-Pick type C disease (NPC). Miglustat has also been approved for NPC treatment in Australia, Brazil, Canada, Israel, Turkey and Switzerland.[26,27]

10.3 Pharmacokinetics and drug metabolism. In studies of miglustat in Gaucher disease patients the time to maximum observed plasma concentration was 2 to 2.5 hours. Plasma concentrations declined biexponentially, with a short distribution phase followed by a longer elimination phase. The half-life of miglustat is approximately 6-7 hours. Steady state is achieved by 1.5 to 2 days after initiation of 3 times daily dosing.[26]

10.4 Miglustat oral bioavailability. The mean oral bioavailability of miglustat capsules is approximately 97%.[26]

10.5 Miglustat distribution. In studies of patients with Gaucher disease type I, the mean apparent volume of distribution of miglustat is 83-105 liters, indicating significant distribution into extravascular tissues.[27]

A pharmacokinetic profile study of miglustat in healthy rats showed miglustat to be well absorbed after a single oral administration with an oral bioavailability of 40-60%. Miglustat is eliminated renally by glomerular filtration and active secretion. Hepatic clearance of miglustat was shown to be negligible. Miglustat was found to have good partitioning into most tissues evaluated, including bone marrow, lungs, heart, kidney, bladder, liver, stomach, and small and large intestine. Miglustat showed appreciable distribution into the rat brain tissue. The ratio of tissue:plasma AUC for the rat brain was 0.40. Miglustat elimination half-life in the rat plasma was approximately 5 hours, but was significantly longer in the brain tissue at 17 hours.[20]

10.6 Miglustat elimination. The major elimination route for miglustat is renal. Miglustat is excreted unchanged in the urine.[26]

10.7 Renal insufficiency. In adult Gaucher disease patients, initial starting dose may be reduced to 100 mg twice daily for creatinine clearance 50-70 ml/min/1.73 m^2; 100 mg once daily for 30-50 ml/min/1.73 m^2; and miglustat is not recommended for Gaucher patients with renal clearance less than 30 ml/min/1.73 m^2.[26]

10.8 Hepatic disease. Miglustat is not metabolized and no dose adjustments are needed for hepatic function impairment.[26]

10.9 Toxicology. The most common adverse effects of miglustat in adult Gaucher disease type I are gastrointestinal side effects of diarrhea (up to 100% of patients), flatulence (29-50% of patients), weight loss (39-67% of patients), abdominal pain (18-67% of patients), and benign intentional tremor (up to 33% of adult Gaucher disease type I patients).[25] The gastrointestinal side effects are due to miglustat's inhibition of the action of disaccharidase digestive enzymes in the gut, primarily maltase, sucrose, and to a lesser degree, lactase. The disaccharidase inhibition can cause side effects of osmotic diarrhea when patients eat dairy foods, starchy foods such as bread, pasta and potatoes, and foods containing a high amount of sugar.[26,27] Overdoses in adults lead to neutropenia, which predisposes to severe infection.

There is limited human experience in the use of miglustat in children (especially those less than 4 years of age); as well as known risks of peripheral neuropathy, diarrhea and weight loss. Thrombocytopenia is a known side effect, so prior to surgery or invasive procedures, the child will require a CBC to ensure that the procedure can be safely performed.

Miglustat is in pregnancy risk category C in the USA. There are no adequate, well controlled studies of miglustat in pregnant women. In female rats given miglustat at doses of 20,60,180 mg/kg/day beginning 14 days before mating and continuing through day 17 gestation, decreased live births, decreased birth weight and complete litter loss was observed in the mid- to high-dose groups.[26] In the pregnant rats in the mid- to high-dose groups, delayed parturition and dystocia were also observed.[26]

10.10 Dosing guidelines. Subjects with body surface area (BSA) < 0.73 m^2 will receive the goal dose of 100 mg miglustat three times daily, or the maximum dose tolerated up to 100 mg miglustat three times daily.

Rationale: studies of miglustat in infants and young children with gangliosidosis diseases have shown safety and tolerability. (References: (1) Maegawa GH, van Giersbergen PL, Yang S, Banwell B, Morgan CP, Dingemanse J, Tifft CJ, Clarke JT. Pharmacokinetics, safety and tolerability of miglustat in the treatment of pediatric patients with GM2 gangliosidosis. *Mol Genet Metab.* 2009 Aug;97(4):284-291; (2) Bembi B, Marchetti F, Guerci VI, Ciana G, Addobbati R, Grasso D, Barone R, Cariati R, Fernandez-Guillen L, Butters T, Pittis MG. Substrate reduction therapy in the infantile form of Tay-Sachs disease. *Neurology.* 2006 Jan 24;66(2):278-280; (3) Maegawa GH, Banwell BL, Blaser S, Sorge G, Toplak M, Ackerley C, Hawkins C, Hayes J, Clarke JT. Substrate reduction therapy in juvenile GM2 gangliosidosis. *Mol Genet Metab.* 2009 Sep-Oct;98(1-2):215-224.)

The safety, tolerability and pharmacokinetic study cited above (by Maegawa et al. 2009) showed safety and tolerability of miglustat in eleven children with GM2 gangliosidosis. In this study six of the patients had infantile phenotype (with ages ranging between 1 year and 5 years and BSAs ranging between 0.4 m^2 and 0.7 m^2), and five patients had the juvenile phenotype (with ages ranging between 10.1 years and 20 years and BSAs ranging between 0.8 m^2 and 1.8 m^2).

The dosing of miglustat in the Maegawa study was described as follows: "In order to achieve adequate levels of miglustat in the central nervous system, the highest doses already examined in LSDs [lysosomal storage diseases] were chosen. The drug was administered at a maximum dose of 600 mg/day, divided into three doses. As the study was performed in a pediatric population, the dose was adjusted to the body surface area (BSA) of each patient." Children with BSA < 0.8 m^2 received miglustat dosed at 50 mg-90 mg 3 times daily, titrated to the maximum tolerated dose (up to 270 mg per day). The major dose-limiting drug-related adverse events that resulted in dose reductions of miglustat in Maegawa's study were gastrointestinal side effects secondary to miglustat's inhibition of disaccharidases in the gut, resulting in intolerance of dietary carbohydrates. For patients with BSA < 0.8 m^2, final doses, after titrating to maximum tolerated dose, ranged widely from 360 mg/m^2 to 450 mg/m^2, and the milligrams administered per day ranged from 15 mg/kg/day to 20.9 mg/kg/day.

Subjects with BSA 0.8 – 1.3 m^2 will receive the goal dose of 100 mg miglustat three times daily, or the maximum dose tolerated up to 100 mg miglustat three times daily.

Rationale: In Maegawa's 2009 study, patients with BSA within 0.8 m^2 to 1.3 m^2 received 100 mg 3 times daily.

Subjects with BSA > 1.3 m^2 will receive the maximum dose tolerated, up to 200 mg miglustat three times daily.

Rationale: In Maegawa's 2009 study, patients with BSA > 1.3 m^2 received 600 mg per day (200 mg 3 times daily), or the maximum tolerated dose, up to 200 mg 3 times daily.

10.11 Use of miglustat in this study. Before starting miglustat, patients will be initiated on the ketogenic diet, with goal of achieving a 4:1 ratio, and showing stability on the ketogenic diet for 2 weeks before starting miglustat therapy.

Miglustat dose will be prepared by dissolving contents of one 100 mg capsule in 10 ml of water. Only one dose of miglustat will be prepared at a time and the preparation must be used immediately and not stored for future use. Any unused solution during the initial dose escalation should be discarded. Miglustat dose will be prepared by patient's caregiver and caregiver will be counseled on pregnancy category C status and sperm parameter studies of miglustat. Caregiver should use a mask and gloves during preparation of miglustat solution.

The following written instructions will be given to the parents:

The miglustat dose will be prepared by dissolving contents of one 100 mg capsule in 10 ml of water in a medication dosing syringe. The child's parents will be taught by the study investigator how to measure the 10 ml of water and mix with miglustat powder in the syringe prior to administration. Only one dose of miglustat will be prepared at a time and the preparation must be used immediately and not stored for future use. Any unused solution during the initial dose escalation should be discarded. Parent should use a mask and gloves during preparation of miglustat solution.

10.12 Miglustat dose titration schedule.

For subjects with a BSA of < 1.3 m^2, the goal dose will be 100 mg three times daily.

The miglustat dose will be titrated over approximately 8 weeks to a goal dose of 100 mg 3 times daily in pediatric patients in this study, according to the following titration schedule:

The contents of one 100 mg capsule will be dissolved in 10 ml water and then 5 ml of this solution (50 mg, dissolved in 5 ml water), will be administered once daily in the evening for two weeks.

If the 50 mg once daily dose is well tolerated (i.e., patient does not show signs of gastrointestinal side effects of diarrhea, reflux or gastrointestinal cramping), then the dose will be increased to 100 mg once daily for two weeks.

The 100 mg dose will be prepared by dissolving contents of one 100 mg capsule in 10 ml of water, followed by administration of the 100 mg dose (dissolved in the 10 ml water) once daily in the evening for two weeks.

If the 100 mg once daily dose is well tolerated (i.e., patient does not show signs of gastrointestinal side effects of diarrhea, reflux or gastrointestinal cramping), then the dose will

be increased to 100 mg twice daily for two weeks. Each 100 mg dose will be prepared by mixing contents of one 100 mg capsule in 10 ml of water for each dose, and using each dose immediately after preparation (do not save any unused portion of the mixture).

If the 100 mg twice daily dose is well tolerated (i.e., patient does not show signs of gastrointestinal side effects of diarrhea, reflux or gastrointestinal cramping), then the dose will be increased to 100 mg three times daily for two weeks. Each 100 mg dose will be prepared by mixing contents of one 100 mg capsule in 10 ml of water for each dose, and using each dose immediately after preparation (do not save any unused portion of the mixture).

If the dose of 100 mg three times daily is well tolerated (i.e., patient does not show signs of gastrointestinal side effects of diarrhea, reflux or gastrointestinal cramping), then the dose will continue at 100 mg three times daily.

If the subject's BSA is > 1.3 m^2, and if their insurance covers up to 600 mg/day miglustat, if the dose of 100 mg three times daily is well tolerated for two weeks, then increase dose to 100 mg in the morning and at midday and 200 mg in the evening for two weeks. If this dose is well tolerated, then increase dose to 200 mg in the morning, 100 mg at midday and 200 mg in the evening for two weeks. If this dose is well tolerated, then increase dose to 200 mg in the morning, 200 mg at midday and 200 mg in the evening for two weeks. If the dose of 200 mg three times daily is well tolerated (i.e., patient does not show signs of gastrointestinal side effects of diarrhea, reflux or gastrointestinal cramping), then the dose will continue at 200 mg three times daily.

If the subject's BSA is > 1.3 m^2, but the subject's insurance does not cover miglustat dose of 200 mg three times daily, subject will use maximum dose of miglustat that is covered by the subject's insurance, not to exceed 600 mg/day miglustat.

10.13 Dose adjustment guidelines:

Peripheral neuropathy: If a patient is found to have peripheral neuropathy that is increased above pre-treatment levels, the dose of miglustat will be reduced by one-third and patient will be reassessed by neurologist 1 month later. If peripheral neuropathy has not resolved, the miglustat dose will be reduced by another one-third and the patient evaluated again after 1 month. If peripheral neuropathy continues, at the discretion of the neurologist, miglustat may be stopped.

Thrombocytopenia: If a patient is found to have thrombocytopenia, the dosing of miglustat will be held and CBC with platelets and differential checked weekly until platelet count recovers. If platelet counts do not recover after 2 weeks, then at discretion of study physician, miglustat therapy may be stopped, if deemed necessary under clinical discretion of study physician.

Gastrointestinal side effects of miglustat: If a patient is having gastrointestinal side effects of nausea, vomiting, reflux, cramping, or diarrhea, the study doctors and ketogenic diet team will evaluate if there is a miglustat-carbohydrate interaction occurring that may involve too many carbohydrates in the diet, requiring dietary adjustments; and/or whether there are medications that patient may be taking that contain high levels of carbohydrate (i.e., liquid solution formulation of anti-seizure medications that are manufactured using simple syrup formulations). Medications made with high carbohydrate components such as simple syrups will need to be changed to unsweetened liquids or changed to a tablet or capsule form that may be crushed and administered via feeding tube. The study doctor will work with the patient's ketogenic diet

team to make these changes. If no dietary or medication cause of gastrointestinal side effects is found, miglustat should be stopped to see if symptoms resolve. If symptoms resolve after stopping miglustat, miglustat may be re-started at 50 mg once daily, and, if tolerated with no gastrointestinal side effects, the dose may be slowly titrated as tolerated, to goal dose or maximum dose tolerated, not to exceed goal dose for patient's BSA.

11.0 Ketogenic Diet

11.1 Description and approved uses. The ketogenic diet is a high-fat, low-carbohydrate diet that is an established and effective non-pharmacologic treatment for epilepsy in children.[28-30] A highly restricted Ketogenic diet, or 4:1 ketogenic diet, is often the form of the diet used for recalcitrant seizures and consists of 4 grams of fat to 1 gram of combination of protein and carbohydrate.[28-30]

11.2 Toxicities. The ketogenic diet has been safely used in children and adults for many decades.[28-30] Patients may experience constipation with use of the ketogenic diet, especially during the initiation phases of the ketogenic diet.[28-30] Patients should be monitored for hypoglycemia 2 to 3 times daily during the initiation of the ketogenic diet, more frequently during adjustments to the ketogenic diet, and then periodically after they are stabilized on the ketogenic diet, as deemed appropriate by the patient's clinical ketogenic diet team.[28-30] A rare side effect of the ketogenic diet is increased risk of kidney stone formation.[28-30] Ketogenic diets, when properly followed, have not shown adverse effects on lipid profiles, but due to the higher fat content of the ketogenic diet, plasma lipid profiles should be monitored every 6 months.[28-30] Some patients have experienced a transient increase in seizures during the initiation of the ketogenic diet.[28-30]

11.3 Use of ketogenic diet in this study. The ketogenic diet may provide benefits for patients with gangliosidoses by the following mechanisms:

1) Minimize or reduce the severity of food-drug interactions between miglustat and carbohydrates
2) Reduce seizure activity
3) Increase the bioavailability of miglustat to the central nervous system

11.4 Initiation and management of the ketogenic diet. The ketogenic diet must be initiated and managed by a clinical ketogenic diet team. Members of this team will include a ketogenic dietician and neurologist trained in the ketogenic diet. The ketogenic diet team will work in collaboration with the patients' doctor Chester Whitley, MD, PhD, Pediatric Geneticist and Primary Care Pediatrician; and Dr. Jeanine R. Jarnes, Clinical PharmD. The patients will be admitted to hospital for 2-3 days for initiation of the ketogenic diet, during which time the goal will be to transition them from their previous diet to a 1:1 ketogenic diet, and then to a 2:1 ketogenic diet. During hospitalization, urine or plasma ketones and blood glucose will be monitored per the institution's policy for ketogenic diet initiation, and the caregivers will be taught how to do home urine ketone monitoring and home blood glucose testing. The patient may be further transitioned to a 3:1 and then to a 4:1 ketogenic diet after discharge from the hospital. Ketogenic diet management will be performed not only at the University of Minnesota, but also locally by a local ketogenic diet team that works in close communication with the University of Minnesota ketogenic diet team. This teamwork relationship will be established prior to the subject beginning their transition to the ketogenic diet at the University of Minnesota. Communication between the two ketogenic diet teams will occur prior to the subject beginning

their transition to the ketogenic diet at the University of Minnesota, and will recur weekly during the period in which the child is transitioning to the ketogenic diet, as well as whenever questions arise.

The ketogenic diet can cause constipation. The ketogenic diet may also cause increased urination, and this could lead to dehydration. Subjects may experience lethargy while transitioning to the ketogenic diet. The lethargy often resolves once the patient is established on the ketogenic diet, but in some patients it may continue. A rare adverse effect of the ketogenic diet is the development of kidney stones.[28-30] Anti-seizure medications that are classified as carbonic anhydrase inhibitors (e.g., acetazolamide, topiramate) have been associated with the development of kidney stones on rare occasions.[31] Patients using anti-seizure medications that are classified as carbonic anhydrase inhibitors may be at increased risk of development of kidney stones.[31] Ensuring adequate hydration and avoiding use of anti-seizure medications that are carbonic anhydrase inhibitors will help minimize risk of kidney stone formation.[31]

11.5 Other parameters being monitored. The following parameters will be monitored at baseline and then every 3 months for the first year of treatment, and then every 6 months thereafter: subject weight, height, occipital-frontal circumference, comprehensive metabolic panel (including serum creatinine and estimated GFR and liver function tests), CBC with platelets and differential, lipid panel, neurologic exam to assess for peripheral neuropathy, and urine pregnancy test in all post-pubertal females. It is acceptable for this interval safety monitoring to not occur at the primary study site as long as the neurologic exam could be performed by an experienced practitioner.

12.0 Study Objectives

12.1 Primary objective. The primary analysis for Syner-G treatment regimen will use the intention-to-treat (ITT) population and evaluate overall survival. This will be evaluated based on chronological age at time of death or conclusion of study (whichever occurs first), and compared to available natural history data. Median survival will be compared to previously reported natural history studies of infantile[9] and juvenile[11] forms. Median survival of patients with infantile GM2 gangliosidosis was estimated at 47 months based on data from the National Tay-Sachs and Allied Diseases database for patients born after 2000.[9] Median survival for the juvenile form was estimated at 14.5 years.[11]

12.2 Secondary objective. Evaluate the effect of Syner-G therapy in patients with infant and juvenile gangliosidoses on changes in neurodevelopmental status, as assessed using age-equivalent scores of the Bayley Scales of Infant and Toddler Development for expressive communication, receptive communication, fine motor skills and gross motor skills; and using the Vineland Adaptive Behavior Scales.

A secondary endpoint will be the rate of change (i.e., slope) in neurocognitive functioning over the duration of follow-up, compared to available natural history data. This analysis will be conducted separately for each of the two sub-types: infantile and juvenile. The primary neurocognitive functioning endpoint for both pediatric groups is age-equivalent scores of the Bayley Scales of Infant and Toddler Development for expressive communication, receptive communication, fine motor skills and gross motor skills. Another primary neurocognitive functioning endpoint for both pediatric groups is age-equivalent scores of the Vineland Adaptive Behavior Scales. Using general estimating equations (GEE) and an exchangeable working correlation structure, variance estimation for confidence intervals and P-values will take into

account the possible correlated nature of multiple measurements on the same individual. Supportive analyses will include evaluation using the per-protocol (PP) population.

13.0 Study Design

13.1 Overview of study design. Both retrospective and prospective data will be collected during this study. This is a single-arm treatment protocol, with intention-to-treat per-protocol design. The primary analysis for Syner-G treatment regimen will use the intention-to-treat (ITT) population and evaluate overall survival. This will be evaluated based on chronological age at time of death or conclusion of study (whichever occurs first), and compared to available natural history data. This will be conducted separately for each of the two sub-types: infantile and juvenile. The neurocognitive functioning endpoint for both groups is the cognition domain of the Bayley Scales of Infant and Toddler Development for expressive communication, receptive communication, fine motor skills, gross motor skills; and the Vineland Adaptive Behavior Scales. Each of the other 4 domains will be evaluated as secondary endpoints. Using general estimating equations (GEE) and an exchangeable working correlation structure, variance estimation for confidence intervals and P-values will take into account the possible correlated nature of multiple measurements on the same individual. Supportive analyses will include evaluation using the per-protocol (PP) population.

Subgroup analyses: analyses will be repeated among GM1 gangliosidosis patients and among GM2 gangliosidosis patients, and among the infantile and juvenile forms of both GM1 and GM2 gangliosidosis.

Yearly evaluations, whenever possible, will also explore changes in seizure frequency and severity, and in movement disorders, evaluated by neurologist and parent-report.

Some subjects do not have insurance coverage for certain evaluations. Sometimes the insurance coverage changes and clinical care that was covered in the past is no longer covered. The investigators will continue to see these patients annually, whenever possible, and will provide the scheduled clinical-care visits according to what is allowed within the restrictions of the subject's health care insurance. When any given subject is unable to make their annual visit to the University of Minnesota due to illness or weakness, this will not cause them to be withdrawn from the research study. The reason for foregoing the evaluation will be documented in the subject's file, and the investigators will continue to follow them through telephone contacts with family members and health care providers.

13.2 Study population. Study population will be any patient with an infantile or late-infantile/juvenile gangliosidosis disease.

13.3 Sample size. A total of 30 infants or children:

- 5 patients with infantile Tay-Sachs disease
- 5 patients with juvenile Tay-Sachs disease
- 5 patients with infantile Sandhoff disease
- 5 patients with juvenile Sandhoff disease
- 5 patients with infantile GM1 gangliosidosis
- 5 patients with juvenile GM1 gangliosidosis

13.4 Subject recruitment. Subjects will be recruited from the investigators' clinical practice and through the Lysosomal Disease Network. This clinical trial will be posted on ClinicalTrials.gov and this may serve to recruit patients to the study.

13.5 Subject screening. Eligibility will be assessed during a baseline evaluation and will include confirmation of gangliosidosis disease via mutation analysis and tissue (e.g. leukocyte) ascertainment of level of hexosaminidase or β-galactosidase enzyme activity.

13.6 Prior and concomitant therapy. Subjects may have had previous therapies for gangliosidosis. If subjects are taking miglustat and/or pyrimethamine, and/or are on a ketogenic diet at the time of screening, they will be allowed to continue these therapies and will be allowed to participate in the Syner-G study.

13.7 Inclusion criteria. Subjects will be eligible to participate in the study if all of the following criteria are met: 1) confirmed diagnosis of infantile or juvenile GM1or GM2 gangliosidosis via mutation analysis and tissue enzyme activity analysis (e.g. leukocyte activity of β-hexosaminidase A, including percent activity contributed from both α–subunit and β–subunits) or tissue β-galactosidase enzyme activity; 2) subjects must be age 0 - 17 years at time of enrollment; and 3) subjects and their caregivers must work closely with their University of Minnesota ketogenic diet team, and with their local ketogenic diet team, which must include a ketogenic dietician and a neurologist trained in the ketogenic diet.

13.8 Exclusion criteria. Subjects will not be eligible to participate in the study if any of the following criteria are met: 1) a desire to not participate; 2) children with severe renal impairment will be excluded from the study; 3) post-pubertal females who are pregnant or unwilling to use highly-effective methods to prevent pregnancy will be excluded from the study; 4) breast-feeding females will be excluded from this study; and 5) subjects who have an allergy to miglustat or any of the components within the drug product will be excluded from this study.

13.9 Exit/discontinuation criteria. Subjects will exit the study if any of the following conditions exist: 1) subject voluntarily withdraws from the study; 2) subject acquires any of the listed exclusion criteria; 3) subject develops severe renal impairment; 4) subject becomes pregnant; or subject's well-being, in the opinion of the Investigator, would be compromised by study continuation.

14.0 Informed Consent

All subjects and their parents or caregivers for this study will be provided a University of Minnesota IRB-approved consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the University of Minnesota IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. A blank copy of the IRB-approved form must be kept on-site and by the sponsor-investigator.

15.0 Laboratory Testing Procedures

All labs will be sent to Fairview Labs for in-house processing, or to be forwarded by Fairview Labs to outside processing facilities:

Fairview Diagnostic Laboratories
Mayo Building Room D293
420 Delaware St SE (MMC 300)
Minneapolis, MN 55455
612-273-7838 voice, 612-273-0183 fax

15.1 Other parameters being monitored. The following parameters will be monitored at baseline and then every 3 months for the first year of treatment, and then every 6 months thereafter: subject weight, height, occipital-frontal circumference, comprehensive metabolic panel (including serum creatinine and estimated GFR and liver function tests), CBC with platelets and differential, lipid panel, neurologic exam to assess for peripheral neuropathy, and urine pregnancy test in all post-pubertal females. It is acceptable for this interval safety monitoring to not occur at the primary study site as long as the neurologic exam could be performed by an experienced practitioner.

16.0 Subject Withdrawal

16.1 How to withdraw subjects. Patients can choose to withdraw from the study at any time. We will request that the patients notify the investigators if they wish to withdraw from the study. Subjects will stop the study if:

1) The subject voluntarily chooses to withdraw from the study.
2) The study investigator(s) may choose to discontinue patient from study if patient is experiencing adverse effects that cannot be managed by dose adjustments of the study agent.

16.2 Data collection and follow-up for withdrawn subjects. Patients will continue to receive full clinical services in our lysosomal disease treatment clinic.

16.3 Subject compensation. There will be no compensation to subjects for participation in this clinical trial.

17.0 Study Timetable / Schedule of Events

BL = Baseline, Wk = Week, M = Month, Y = Year

Study Events	Pre-Study	BL	Wk 1	Wk 2	Wk 3	M 1, Wk 4	M 3	M 6	M 9	Y 1 M 12	M 18	Y 2-5 Annual Visits	Y 2-5 Half-Year Time-Point	Every 3 M Throughout this Research Study	Monthly Assessment after the First Year of Study Participation
Determination of leukocyte hexosaminidase activity level for GM_2 gangliosidosis patients, or β-galactosidase activity level for GM_1 gangliosidosis patients	X														
Informed Consent		X													
Demographics data collection		X													
Retrospective data collection		X													
Telephone follow-up call: In addition to the timetable shown here, a member of the study staff will contact the parent *at least* once weekly during the time when the subject is transitioning onto the ketogenic diet, and while the subject is titrating the miglustat dose, and any time the dose is decreased due to adverse events, until symptoms have re-solved. Additionally, while the subject is on a stable (goal) miglustat dose, side effects will be assessed by telephone contact or at clinic visits every 3 months throughout the study period.		X	X	X	X	X	X	X	X	X	X	X	X	X	
Miglustat goal dose = 100 mg 3X daily. Evaluation of dose titration and tolerance of miglustat therapy by tele-phone contact and during clinic visit. After 1st year, assessments will continue for a minimum of once monthly.			X	X	X	X	X	X	X	X	X	X	X		X
Ketogenic Diet 4:1 Evaluation by ketogenic dietician and neurologist trained in ketogenic diet (a "ketogenic diet team") per institution's clinical program protocol, either at the research site or locally in subject's geographic area. After 1st year, assessments will continue for a minimum of once monthly.		X	X	X	X	X	X	X	X	X	X	X	X		X
Neuropsychological Testing changes in neuropsychiatric status as assessed by: age-equivalent scores of Bayley Scales of Infant and Toddler Development; and of Vineland Adaptive Behavior Scales		X								X		X			
Neurological evaluation of changes in seizure frequency and severity, and of movement disorders		X								X		X			
Measurement of subject weight, height, occipital-frontal circumference, comprehensive metabolic panel (including serum creatinine, estimated GFR, and liver function tests), CBC with plate-lets and differential, lipid panel, neurologic exam to assess for peripheral neuropathy, and urine pregnancy test in all post-pubertal females. It is accept-able for this interval safety monitoring to not occur at the primary study site as long as the neurologic exam is performed by an experienced practitioner.		X					X	X	X	X	X	X	X		

Whenever possible, the scheduled assessments/exams will be conducted on all subjects for the duration of the study. However, due to disease progression or concurrent illness, some patients after enrollment may not be able to fulfill the annual visit requirement. If this occurs, a failure to appear for any given annual visit will not make any subject ineligible to continue as a research participant. For research purposes, the rarity of the gangliosidoses dictates that as much data as possible be collected on any given subject.

When any newly-enrolled subject is already using the Syner-G regimen at time of enrollment, for clinical management, the Schedule of Events for that subject will begin with the scheduled time-point that corresponds to the number of weeks or months that subject has been using Syner-G.

18.0 Data Analysis

18.1 Subject populations for analysis:

- Intention-to-treat Population (ITT): All subjects who initiate any portion of the treatment regimen in association with this study
- Per-protocol Population (PP): Includes all subjects who initiate treatment and are compliant with at least 75% of prescribed drug doses of miglustat, and at least 3:1 ketogenic diet.
- Safety population: All subjects who receive any amount of the combination treatment regimen. Due to the nature of a combination treatment, multiple groups may be identified, should partial adherence be observed.

18.2 Sample size determination. The sample size for the study was determined primarily by feasibility due to the extremely rare nature of the disease. There are two distinct sub-types to be evaluated: infantile and juvenile. Analysis will be based on variability estimates from published natural history studies[8,11,19] of the infantile form and juvenile form, and correlation between baseline and annual follow-up for up to 4 years.

18.3 Statistical analysis. Descriptive analyses of baseline characteristics and outcomes will include means, standard deviations, medians, and ranges for continuous variables and frequencies for categorical variables. Treatment compliance for each group will also be evaluated. All analyses will be conducted separately for the two disease sub-types – infantile and juvenile – due to the highly heterogeneous patient groups.

The primary analysis for Syner-G treatment regimen will use the intention-to-treat (ITT) population and evaluate overall survival. This will be evaluated based on chronological age at time of death or conclusion of study (whichever occurs first), and compared to available natural history data. Median survival will be compared to previously reported natural history studies of infantile[9] and juvenile[11] forms. Infantile median survival was estimated at 47 months based on data from the National Tay-Sachs and Allied Diseases database for patients born after 2000.[9] Median survival for the juvenile form was estimated at 14.5 years.[11]

A secondary endpoint will be the rate of change (i.e., slope) in neurocognitive functioning over the duration of follow-up, compared to available natural history data. This analysis will be conducted separately for each of the two sub-types: infantile and juvenile. The primary

neurocognitive functioning endpoint for both pediatric groups is age-equivalent scores of the Bayley Scales of Infant and Toddler Development for expressive communication, receptive communication, fine motor skills and gross motor skills. Another primary neurocognitive functioning endpoint for both pediatric groups is age-equivalent scores of the Vineland Adaptive Behavior Scales. Using general estimating equations (GEE) and an exchangeable working correlation structure, variance estimation for confidence intervals and P-values will take into account the possible correlated nature of multiple measurements on the same individual. Supportive analyses will include evaluation using the per-protocol (PP) population.

Safety analyses will be primarily descriptive, reporting the number and percentage of AEs and descriptive summaries. These analyses will use multiple safety populations according to which components of the combination therapy subjects were exposed to. Due to the longitudinal nature of the study and potential for later-emerging effects, the safety profile will be characterized for each sub-type over time. Supportive analyses will include evaluation using the PP population.

Subgroup analyses: analyses will be repeated among GM1 gangliosidosis patients and among GM2 gangliosidosis patients, and among the infantile and juvenile forms of both GM1 and GM2 gangliosidosis.

18.4 Missing data. Despite best efforts to avoid missing data, it is possible that some will occur and will be a potential limitation to the interpretation and generalizability of results. In particular, missing data may arise for non-survival outcomes (e.g. neurocognitive function data) in the event of death. For these instances, it is unclear whether a complete-case analysis (i.e. excluding patients who die) would be unbiased, and therefore would be unsatisfactory. It is also unclear what would be an appropriate magnitude of discount to satisfactorily represent the negative outcome of death. By conducting both the complete-case analysis (unbiased if death is independent of the non-survival outcome) and an analysis with an imputed value for instances of death (intention-to-treat type of analysis), the potential magnitude of treatment effect will be better characterized.

Missing data may also arise from “lost to follow-up.” The last-observation-carried-forward imputation will be used to satisfy this type of missing data. Sensitivity analyses to evaluate the extent to which results are dependent on the approach to missing data will be conducted, wherein multiple imputations will also be considered.

19.0 Safety Monitoring

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to University of Minnesota IRB for approval. Participant enrollment may only proceed with IRB approved consent forms. All adverse events will be reported to the local IRB and to the Study Chair who will tabulate and review these events.

The Study Chair has primary oversight responsibility of this clinical trial. The Study Chair and the Steering Committee will review accrual patterns, adverse events, data quality, and protocol compliance.

19.1 Data and safety monitoring plan. The NINDS has reviewed the risk associated with this study, and the following safety monitoring will be implemented:

The Study Chair and her IRB will monitor the study and all adverse events. In addition, adverse event reports will be sent to the ORDR-designated medical monitor on a basis to be agreed upon, generally monthly. The ORDR-designated medical monitor will also review cumulative adverse events (AEs). The frequency of review of cumulative AEs will be determined by the medical monitor in conjunction with the Study Chair and will occur at least every 12 months.

The Study Chair has primary oversight responsibility of this clinical trial. The investigators will identify adverse events on an ongoing basis as they occur and will report them to the IRB and the Data Management and Coordinating Center (DMCC). If a subject experiences an adverse effect from the treatment medication, dose reduction adjustments will be made to the medication, if indicated.

The Principal Investigator and the research team (co-investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report–detailed by severity, attribution (expected or unexpected), and relationship to the study procedures–will be available from the DMCC for site review. Adverse events will be reviewed by the research team as they occur. A separate report detailing protocol compliance will also be available from the DMCC for site review on a monthly basis. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

19.2 Adverse event definitions and standards. The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defect."

An unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks described in the protocol.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

19.3 Expected and known risks, discomforts, or adverse events associated with study intervention and procedures: Definition of expected adverse events. Neuropsychological testing: No known risks. No sensitive questions will be asked during the testing.

Anticipated risks of miglustat.[23] Potential risks to subjects include the following adverse drug events:

In clinical trials of miglustat in children with gangliosidoses, miglustat demonstrated an acceptable safety profile for use in young children. The most common side effects reported

were diarrhea and weight loss. These gastrointestinal side effects of miglustat may be prevented or ameliorated by using a low-carbohydrate diet.

In clinical trials of adult patients with Gaucher disease type I, common side effects reported included:

- Diarrhea (up to 100% of patients of patients with adult Gaucher disease type I)
- Flatulence (29-50% of patients of patients with adult Gaucher disease type I)
- Weight loss (39-67% of patients of patients with adult Gaucher disease type I)
- Abdominal pain (18-67% of patients of patients with adult Gaucher disease type I)
- Tremor (11-30% of patients with adult Gaucher disease type I)

Miglustat risk mitigation. Risks of gastrointestinal side effects may be mitigated by implementation of a ketogenic diet that may minimize or reduce the severity of food-drug interactions between carbohydrates and miglustat.

Anticipated risks of the ketogenic diet. The ketogenic diet has been safely used in children and adults for many decades.[28-30] Patients may experience constipation with use of the ketogenic diet, especially during the initiation phases of the ketogenic diet. The ketogenic diet may also cause increased urination, and this could lead to dehydration. Subjects may experience lethargy while transitioning to the ketogenic diet. The lethargy often resolves once the patient is established on the ketogenic diet, but in some patients it may continue. Patients should be monitored for hypoglycemia 2 to 3 times daily during the initiation of the ketogenic diet, more frequently during adjustments to the ketogenic diet, and then periodically after they are stabilized on the ketogenic diet, as deemed appropriate by the patient's clinical ketogenic diet team. A very rare occurrence of kidney stones in patients using the ketogenic diet has raised a concern about the possibility of an increase in risk of kidney stone development.[28-30] Increased risk of kidney stones has been associated with anti-seizure medications that have carbonic anhydrase inhibiting action, such as acetazolamide and topiramate.[31] Some patients have experienced a transient increase in seizures during the initiation of the ketogenic diet.[28-30]

Risk mitigation of the ketogenic diet. The ketogenic diet will be managed by a clinical ketogenic diet team that includes ketogenic dietician(s), neurologist, pharmacist and clinical geneticist, specially trained in the implementation and maintenance of the ketogenic diet. The ketogenic dietitian will make recommendations for ordering of nutrition labs and lipid labs prior to beginning ketogenic diet and as clinically indicated (e.g. lipid panel, comprehensive metabolic panel, transferrin, pre-albumin, vitamin levels for vitamin D and the B vitamins). Patients will be evaluated for signs of development of constipation or worsening of existing constipation, and will be treated as needed with medications for treatment/prevention of constipation. Subjects will be monitored for signs of dehydration per ketogenic dietitian recommendation, and will be treated as needed with appropriate hydrating fluids per ketogenic dietitian's clinical management and recommendations. Patients will also be monitored for signs of kidney stone development, such as signs of pain and/or difficulty urinating. Use of anti-seizure medications with carbonic anhydrase inhibiting action will be minimized and avoided if possible.[31]

There are no anticipated risks to investigators, lab personnel, and/or the environment.

19.4 Adverse event reporting timeline.

- Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:

- Is considered life-threatening/disabling or results in death of participant

-OR-

- Is Unexpected/Unanticipated

- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the Rare Diseases Clinical Research Network (RDCRN) within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs and the FDA remain the responsibility of the site investigator and the Study Chair.

19.5 RDCRN Adverse Event Data Management System (AEDAMS). Upon entry of a serious adverse event by the site investigator, the DMCC-created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair, the site PI, and the Medical Review Officer of any reported adverse events via e-mail.

Serious adverse events. The NIH appointed Medical Review Officer (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. A back-up notification system is in place so that any delays in review by the MRO beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events. Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the MRO on an annual basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all adverse events (serious/not serious and expected, unexpected) for site investigators and IRBs.

19.6 Unanticipated Problem Reporting. The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given
  - (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
  - (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences, and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

Incidents or events that meet the OHRP criteria for unanticipated problems are to be reported to the IRB, per local institutional reporting requirements. Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

20.0 Anticipated Risks

20.1 Anticipated risks of miglustat.[23] Potential risks to subjects include the following adverse drug events:

In clinical trials of miglustat in children with gangliosidoses, miglustat demonstrated an acceptable safety profile for use in young children. The most common side effects reported were diarrhea and weight loss. These gastrointestinal side effects of miglustat may be prevented or ameliorated by using a low-carbohydrate diet.

In clinical trials of adult patients with Gaucher disease type I, commonly reported side effects of miglustat included:

- Diarrhea (up to 100% of patients of patients with adult Gaucher disease type I)
- Flatulence (29-50% of patients of patients with adult Gaucher disease type I)
- Weight loss (39-67% of patients of patients with adult Gaucher disease type I)
- Abdominal pain (18-67% of patients of patients with adult Gaucher disease type I)
- Tremor (11-30% of patients with adult Gaucher disease type I)

20.2 Miglustat risk mitigation. Risks of gastrointestinal side effects may be mitigated by implementation of a ketogenic diet that may minimize or reduce the severity of food-drug interactions between carbohydrates and miglustat.

20.3 Anticipated risks of the ketogenic diet. The ketogenic diet has been safely used in children and adults for many decades.[28-30] Patients may experience constipation with use of the ketogenic diet, especially during the initiation phases of the ketogenic diet. The ketogenic diet may also cause increased urination, and this could lead to dehydration. Subjects may experience lethargy while transitioning to the ketogenic diet. The lethargy often resolves once the patient is established on the ketogenic diet, but in some patients it may continue. Patients should be monitored for hypoglycemia 2 to 3 times daily during the initiation of the ketogenic diet, more frequently during adjustments to the ketogenic diet, and then periodically after they are stabilized on the ketogenic diet, as deemed appropriate by the patient's clinical ketogenic diet team. A very rare occurrence of kidney stones in patients using the ketogenic diet has raised a concern about the possibility of an increase in risk of kidney stone development.[28-30] Increased risk of kidney stones has been associated with anti-seizure medications that have carbonic anhydrase inhibiting action, such as acetazolamide and topiramate.[31] Some patients have experienced a transient increase in seizures during the initiation of the ketogenic diet.[28-30]

20.4 Risk mitigation of the ketogenic diet. The ketogenic diet will be managed by a clinical ketogenic diet team that includes ketogenic dietician(s), neurologist, pharmacist and clinical geneticist, specially trained in the implementation and maintenance of the ketogenic diet. The

ketogenic dietitian will make recommendations for ordering of nutrition labs and lipid labs prior to beginning ketogenic diet and as clinically indicated (e.g. lipid panel, comprehensive metabolic panel, transferrin, pre-albumin, vitamin levels for vitamin D and the B vitamins). Patients will be evaluated for signs of development of constipation or worsening of existing constipation, and will be treated as needed with medications for treatment/prevention of constipation. Subjects will be monitored for signs of dehydration per ketogenic dietitian recommendation, and will be treated as needed with appropriate hydrating fluids per ketogenic dietitian's clinical management and recommendations. Patients will also be monitored for signs of kidney stone development, such as signs of pain and/or difficulty urinating. Use of anti-seizure medications with carbonic anhydrase inhibiting action will be minimized and avoided if possible.[31]

There are no anticipated risks to investigators, lab personnel, and/or the environment.

21.0 Study Discontinuation

21.1 Discontinuation rules. The NIH and the University of Minnesota IRB have the authority to stop or suspend this study at any time. Additionally, the following study discontinuation rules apply:

1) That the rate of severe adverse events is such that continued participation would compromise subject safety.
2) Target subject accrual has not met, and cannot meet trial objectives.

21.2 Participant discontinuation. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant, and participants will be followed clinically until, if applicable, all adverse events resolve. Participant discontinuation in this study will occur for the following reasons:

- Participants who develop kidney function problems while in this study will be withdrawn from this study.
- Females who are able to become pregnant, and who are sexually active, must use a highly effective birth-control method to prevent pregnancy while in this study. If a participant becomes pregnant while in this study, they will be withdrawn from this study.
- If a patient develops bleeding due to low platelets while in this study, treatment with miglustat will be stopped.
- If a patient develops severe diarrhea and/or weight loss that cannot be managed by changing the ketogenic diet formula or lowering the miglustat dose, the patient will be removed from the study.
- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal of the participant by the Investigator(s) (If a subject experiences an adverse effect from the treatment medication, dose reduction adjustments will be made to the medication, or the subject will be withdrawn from the study, if indicated.)

22.0 Data Quality and Monitoring Measures

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The DMCC will monitor data delinquency on an ongoing basis.

22.1 Missing data. Despite best efforts to avoid missing data, it is possible that some will occur and will be a potential limitation to the interpretation and generalizability of results. In particular, missing data may arise for non-survival outcomes (e.g. neurocognitive function data) in the event of death. For these instances, it is unclear whether a complete-case analysis (i.e. excluding patients who die) would be unbiased, and therefore would be unsatisfactory. It is also unclear what would be an appropriate magnitude of discount, to satisfactorily represent the negative outcome of death. By conducting both the complete-case analysis (unbiased if death is independent of the non-survival outcome), and an analysis with an imputed value for instances of death (intention-to-treat type of analysis), the potential magnitude of treatment effect will be better characterized.

Missing data may also arise from "lost to follow-up." The last-observation-carried-forward imputation will be used to satisfy this type of missing data. Sensitivity analyses to evaluate the extent to which results are dependent on the approach to missing data will be conducted, wherein multiple imputations will also be considered.

23.0 Data Management

As much as possible data quality is assessed at the data entry point using intelligent online data entry via Visual Basic-designed screen forms. Data collection will initially be collected on paper forms and then subjected to checking and rescoring by the individual collecting the data. Following this, data will be entered online to the DMCC database. At the University of Minnesota, data will be entered by the individual collecting the data as well as by our research staff.

All study data will be collected via systems created in collaboration with the RDCRN DMCC and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

23.1 Participant registration. Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data input to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry, since the numbers should match to properly identify the participant. In this fashion, no personal identifiers would be accessible to the DMCC.

23.2 Data entry. Data entry for this study will be accomplished with online electronic case report forms (CRFs). Using encrypted communication links, online forms will be developed that contain the requisite data fields.

23.3 Data quality control. As much as possible data quality is assessed at the data entry point. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. The more important quality assurance measures are the internal validity checks for reasonableness and consistency. In addition to those described above, we propose to build these checks into the initial tables and cross tabulations that should reveal any remaining data quality issues.

23.4 Study records retention. Study records will be maintained for a minimum of two years following the conclusion of the study.

23.5 Protocol deviations. Protocol deviations for this study will be reported per local Institutional guidelines and reporting requirements.

24.0 Human Subjects

24.1 GCP statement. This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

24.2 Risks. The potential risks of this study are:

By participating in this study the subjects will run a slight risk of loss of privacy. The research team will make every effort to protect the subjects by making all of the data that the research team will take from the subjects' records anonymous by identifying it only with a number. Researchers will remove information such as name, address, and phone number, and replace that information with a code number. Only the research investigators will be able to identify which data belong to a given subject; thus the risk is minimal.

None of the neuropsychological tests are in any way harmful for participants, although they may be fatiguing. No embarrassing questions or sensitive stimuli will be used in the neuropsychological testing.

24.3 Benefits. Studies of miglustat in infantile, juvenile and adult gangliosidoses have demonstrated safety, but do not show significant clinical improvement. [23-25] At the University of Minnesota, neuropsychiatric evaluations have shown improvement in some assessed domains for gangliosidosis patients using the goal miglustat dose and the ketogenic diet. Seizure frequency and severity have improved in all the patients; preliminary results suggest further improvement may be possible with the combination of miglustat and the ketogenic diet.

The ketogenic diet may provide benefits for patients with gangliosidoses by the following mechanisms:

1) Minimize or reduce the severity of food-drug interactions between miglustat and carbohydrates

2) Reduce seizure activity
3) Increase the bioavailability of miglustat to the central nervous system.

24.4 Recruitment. Patient recruitment is limited by availability of such patients. All individuals with these disorders will be considered. Disorders may be unevenly prevalent in Ashkenazi Jews, French Canadians, Louisiana Cajuns, and certain old-order Amish. All ethnic and racial groups will be recruited.

24.5 Written and informed consent. Written informed consent will be obtained from each participant before the subject undergoes any study-specific procedures or assessments and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

24.6 Process of consent. At the University of Minnesota the following (from our IRB) will be explained to the patient by an approved member of the research team: consent and assent forms will be given to potential participants prior to enrollment so that they have ample time to review the information and ask questions about the study. Forms can be mailed to the individuals in advance of their participation so that they can read and ask any questions before considering participating. Investigators will ensure that the participant or their legally authorized representative understand the information provided and obtain informed consent. The consenting process will be thoroughly documented in the participants' research charts.

24.7 Certificate of Confidentiality. To help protect participant privacy, a Letter of Confidentiality has been obtained from the National Institutes of Health (NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify a study participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify a participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person.

Department of Health and Human Services (DHHS) personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

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26.0 Appendices and Attachments

26.1 Appendix 1: Informed Consent Forms

Informed Consent documents will accompany this submission, but they are not attached to, nor a part of this Protocol.

26.2 Appendix 2: Neuropsychological Testing Quality Control

1. Neuropsychologists are in possession of all tests and are familiar with administration of each test.
2. Ensure that tests administered are carried out according to specific test instructions. Experienced examiners are available for consultation if there are any questions about administration approaches.
3. When testing is complete, age-equivalent scores will be recorded.
   Data will be input on the online case report forms (CRFs) in the DMCC database using patient identification numbers assigned by Evelyn Redtree, University of Minnesota Research Coordinator.