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

Parental/Guardian Informed Consent for Child

Your child is being invited to participate in a research study to evaluate a combination therapy using miglustat and a ketogenic diet for treatment of the gangliosidoses to learn if this combination therapy approach will provide improved clinical outcomes compared to what we currently know about the natural course of the disease. He/She was selected as a possible participant because they have either GM1 gangliosidosis, Tay-Sachs disease, Sandhoff disease, or other gangliosidosis disease. We ask that you read this form and ask any questions you may have before agreeing to allow your child to be in the study. We anticipate enrolling a total of 30 infants or children who have been diagnosed with a gangliosidosis disease.

This study is being conducted by Dr. Jeanine Jarnes, PharmD, BCOP, BCPS, University of Minnesota, Fairview; and Dr. Chester Whitley, Ph.D., M.D., University of Minnesota, Department of Pediatrics.

Study Purpose

The purpose of the study is to determine if a combination therapy using miglustat and the ketogenic diet for patients with a gangliosidosis disease will:

1) Improve overall survival for patients with infantile and juvenile gangliosidoses compared to previous studies of the natural history of the disease.
2) Improve neurodevelopmental clinical outcomes of therapy compared to previous studies of the natural history of the disease.

Miglustat is not approved for treatment of gangliosidosis diseases, but has been used in this patient population (as outlined in the risks section). This drug is being used because it has been shown to inhibit the production of glycosphingolipids (a substance that builds up in the cells).

The ketogenic diet is indicated for management of seizures in patients with seizure disorders. In this study, the ketogenic diet will be used to minimize or reduce severity of gastrointestinal side effects of miglustat and improve response to miglustat therapy. Patients with infantile and juvenile gangliosidoses commonly suffer from seizure disorders and use of the ketogenic diet in these patients may therefore also improve seizure management.

Study Procedures

If you agree to allow your child to participate in this study, we would ask you to do the following:

- **Blood draws:** Blood samples would be needed before starting the therapy and again at months 1, 3, 6 and 12 months and then every 6 months until the study is completed. Urine ketones and blood glucose will be checked daily to weekly, as needed, during transition to ketogenic diet, and then a minimum of once weekly when the patient is fully transitioned to the ketogenic diet.

- **Miglustat** (also known as Zavesca®) will be used to reduce the amount of ganglioside accumulation in the child's cells. The dose of miglustat will increase every 2 weeks until your child reaches the goal dose for his/her body surface area (BSA). It will take approximately 6 to 12 weeks to reach the full dose of miglustat. This dose titration process may take longer if the child needs more time to adjust to each dose level.

- This drug comes as a capsule. The contents of the capsule will be dissolved in water prior to administration. You will be taught how to prepare this mixture. You will give your child this medication by mouth or through their feeding tube on a very strict schedule starting at 1X per day for 2 weeks, then 2X per day for 2 weeks, then increasing the dose to 3X per day. The dose will be increased every 2 weeks until the goal dose is reached for your child's body surface area (calculated by a formula that uses the child's weight and height). A member of the study staff will contact you at least once weekly during the time when your child is slowly increasing the miglustat dose, to check on how the child is tolerating the miglustat and to help answer questions you may have. If your child is having diarrhea, reflux, or flatulence with signs of discomfort due to abdominal cramping, then we will need to reduce the miglustat dose to a level at which your child shows none of the above gastrointestinal symptoms; and escalate the miglustat dose more slowly.

- **Ketogenic Diet** is a special diet that contains higher amounts of fat and lower amounts of carbohydrate compared to an average diet. The goal is to have 4 parts of fat for every 1 part of protein/carbohydrate. You will work with a ketogenic diet team, that includes a ketogenic dietitian and neurologist, at your local clinic, to help your child to achieve this diet goal. Your child will start with a diet that has 1 part fat and 1 part that contains protein and carbohydrate. The fat part of the diet will be gradually increased by the ketogenic diet team until the goal of 4 parts fat to 1 part containing protein and carbohydrate is achieved.

- The purpose of this special diet is to help minimize or reduce the severity of gastrointestinal side effects of the miglustat and to help reduce seizures. In a study of miglustat combined with a ketogenic diet in mice with a gangliosidosis disease, the combination of ketogenic diet with miglustat resulted in increased concentrations of miglustat in the central nervous system. This study was in in mice and it is unknown if the ketogenic diet will help make the miglustat more effective in the central nervous system in children with gangliosidosis diseases. The study staff will be in communication with your local ketogenic diet team to explain the purpose of the diet for your child and to help answer questions they may have. The study staff will continue to be available to discuss the ketogenic diet with your local ketogenic diet team throughout the study.

During this study, evaluations of your child's gangliosidosis will be completed at baseline and then every 12 months until the study is over in 5 years. These evaluations will be completed at the University of Minnesota. The standard evaluations include:

- **Neurodevelopmental testing** to evaluate his/her neurodevelopmental status. This testing will be done by a Pediatric Neuropsychologist who specializes in evaluating patients with gangliosidosis diseases. The neurodevelopmental testing will take about 3-4 hours.

- **Neurological** evaluation by a neurologist at the University of Minnesota who works with the study staff to assess any seizures or movement disorders. This takes about 1 hour.

Risks of Study Participation

By participating in this study your child runs a slight risk of loss of privacy. We have made every effort to protect him/her by making all of the data that we will take from his/her medical records identifiable only with a number. Only the physicians who are conducting this study will be able to identify which data is your child; thus the risk is minimal.

The study has the following risks:

- **Blood draws** can be uncomfortable and some people develop bruising from the procedure. There is a risk of infection but it is rare.

- **Miglustat:** In clinical trials and through experience using miglustat in children with gangliosidosis diseases, **c**ommon side effects have included diarrhea, gas, abdominal pain, and constipation. If used in conjunction with a very low-carbohydrate diet, the gastrointestinal side effects will be minimized or reduced. In clinical trials of miglustat in adult patients with Gaucher disease type I, common side effects were abdominal pain (18-67%), constipation (8-25%), diarrhea (83-100%), flatulence (29-50%), vomiting (4-11%), headache (21-22%), tremors (11-33%), weight loss (39-67%), dry mouth (up to 8%), muscle cramp (up to 11%), leg cramp (4-11%), dizziness (up to 8%), and visual disturbances (up to 17%). Another adverse event that was reported in clinical trial was a low platelet count (reported in 6%-7% of patients). Low platelets can increase risk of bleeding. There may be adverse effects of miglustat that are not anticipated. You should report any new symptoms or adverse events that your child experiences while on this study. You will be given a name and contact information to report adverse events and symptoms that your child may be experiencing.

- **Ketogenic diet:** The ketogenic diet can cause constipation. We will work with you and your ketogenic diet team to help manage constipation, should it occur. The ketogenic diet may also cause increased urination, and this could lead to dehydration. Your ketogenic diet team will work with you and your child to monitor the hydration status of your child. Patients 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. 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. Patients using anti-seizure medications that are classified as carbonic anhydrase inhibitors may be at increased risk of development of kidney stones. Ensuring adequate hydration and avoiding use of anti-seizure medications that are carbonic anhydrase inhibitors will help minimize risk of kidney stone formation. The ketogenic diet team will work with you and your child to take measures to minimize risk of kidney stones.

Benefits of Study Participation
It is unknown, at this time, what effect, if any, the Syner-G therapy will have on your child's gangliosidosis disease.

Alternatives to Study Participation
You may choose to have your child not participate in the Syner-G study. If you decide not to have your child participate in the Syner-G study, you may continue to have your child evaluated and cared for by the clinicians who are care providers for this study.

Study Costs/Compensation
The evaluations and testing done during this study are part of the University of Minnesota's standard care for patients with gangliosidosis. The evaluations and testing provided during this study will be billed to the patient's medical insurance provider in the usual manner. Participation in this study also allows access to these records by the study team.

There is no compensation for study participation; however, funds may be available to offset the cost of travel to Minneapolis for study participation.

Research Related Injury
We do not expect any injury to occur due to study participation. In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that your child has suffered a research related injury, let the study staff know right away.

Confidentiality
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify your child as a subject. His/her record for the study may, however, be reviewed by representatives of the Food and Drug Administration (FDA), National Institutes of Health (NIH), and by departments at the University with appropriate regulatory oversight. Your child's test and exam results will be recorded in his/her medical record.

The clinical information collected for this study will be stored in a computer database at the Data Management and Coordinating Center (DMCC) at the University of South Florida in Tampa, FL, and also sent to a federal data repository. A data repository provides a way for researchers to store the information collected during the research study for future research studies. The data management center uses several layers of protection for the clinical data stored in its computer database. It meets all of the local and federal security requirements for research datacenters. Your information is stored only using a study ID.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that could identify your child. At most, the web site will include a summary of the results. You can search this web site at any time.
Certificate of Confidentiality (If applicable)

Certificate of Confidentiality
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, 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 you, 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).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious

harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you 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.

We may publish what we learn from this study. If we do, we will not publish your name.

Protected Health Information (PHI)
Your child's PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study
Participation in this study is voluntary. Your decision whether or not to allow your child to participate in this study will not affect his/her current or future relations with the University, Masonic Children's Hospital and Clinics, University of Minnesota Medical Center, Fairview Pharmacy or Clinics. If you decide to allow your child to participate, he/she is free to withdraw at any time without affecting those relationships. If during the course of this research study there are significant new findings discovered which might influence your decision to continue, the researchers will inform you of those developments.

Other Reasons for Stopping the Study
- 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.

Contacts and Questions
The researchers conducting this study are Dr. Jeanine Jarnes, PharmD, and Dr. Chester Whitley, PhD, MD. You or your child/ward may ask any questions you have now, or if you have questions later, you are encouraged to contact them at:

Jeanine Jarnes, PharmD_____(612) 626-5131

Chester Whitley, Ph.D., M.D._____ (612) 625-7422

MMC 446
420 Delaware St. SE
Minneapolis, MN 55455

If you or your child/ward have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may

also contact this office in writing or in person at *Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.*

You will be given a copy of this form to keep for your records.

Statement of Consent

You are making a decision whether or not to allow your child to participate in this study. Your signature indicates that you have read the above information, have received answers to any additional questions you may have had, and have decided to allow him/her to participate. Should you choose to discontinue your child's participation in the study, he/she may withdraw at any time without prejudice after signing this form.

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Printed Name of Subject_____

_____Date_____
Signature of Parent or Guardian

_____Date_____
Signature of Person Obtaining Consent

_____
Printed Name of Person Obtaining Consent

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

You are invited be a part of a study to see if an experimental drug will help with your gangliosidosis condition. You have been invited to join our study because you have been diagnosed with a gangliosidoses condition (GM1 gangliosidosis, Tay-Sachs disease, or Sandhoff disease). To complete this study we will need to look at information in your medical record.

As part of this study, you will be asked to be on a special diet called a ketogenic diet, and to take miglustat, an experimental medication, 3 times daily. Although miglustat is an FDA-approved medication, it is not FDA approved for treatment of gangliosidosis diseases, and for this reason miglustat is considered an investigational agent for this study. Miglustat has been used in patients with gangliosidosis prior to this study, but its use in combination with a ketogenic diet has not been studied in the past.

As part of this study, you will have extra doctor visits and extra blood samples drawn for labs. These extra doctor visits and labs will occur every 3 months during the first year of the study and then every 6 months for 4 more years.

You will also be asked to meet with a doctor once a year to answer a set of questions that allows us to measure your ability to do certain things, such as getting dressed by yourself and buttoning a shirt. These tests will take about 3 to 4 hours to complete. You will be able to take as many breaks as you need. The questions asked will not hurt and we will not ask anything personal or embarrassing.

Side effects of the medication can occur and can include nausea, diarrhea (loose, runny stools), and weight loss. Using the special diet will help reduce the severity of these side effects.

Side effects of the special diet can include tiredness. Side effects of the diet can also include constipation. Your doctors and dietitian will work with you to help reduce and manage side effects. It is possible that side effects will occur that were not expected. It is important that you let your parents and study doctor know if you are having a side effect while in this study.

Your parent or guardian will say it is okay for you to be in this study, but we will not make you join our study if you do not want to join. You can ask us any questions about the study that you want at any time.

Being in this study is up to you. No one will be mad at you or upset if you do not want to be in the study. If you decide to enroll in the study you can stop at any time for any reason. Regardless of whether or not you decide to be in the study, your relationship with your doctors will not change.

<u>Reasons for Stopping the Study</u>
If your kidney function worsens during the study, your doctor will tell you and will stop the miglustat.
If you become pregnant during the study, the miglustat will be stopped.
If you have bleeding or bruising that is severe and is caused by low platelets, the miglustat will be stopped.
The doctors working with you on this study will tell you if you need to stop the study due to side effects that may occur.

If you are sexually active you will need to use a very effective form of birth control during this study in order to prevent pregnancy. Examples of effective contraception include the female partner using a form of a steroid contraceptive agent (oral steroid contraception or intrauterine implanted steroid contraception such as Mirena®), and the male partner using a condom. Both the female and male partner need to use contraception.

Signing here means that you have read this paper or listened to someone read it to you, and you are willing to be in the study. If you don't want to be in the study, then don't sign. Remember, being in the study is up to you, and no one will be upset with you if you don't sign this, or even if you change your mind later.

Participant's signature _____

Date_____

Print participant's name: _____

Signature of person explaining study: _____

Date_____

Title of person explaining study: _____

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

This study is to see if a special medication will help with the management of your gangliosidosis condition. You were selected because you have been diagnosed with a gangliosidoses condition (GM1 gangliosidosis, Tay-Sachs disease, or Sandhoff disease). To complete this study we will need to look at information in your medical record.

This study will last 5 years. You will take a medication called miglustat and go on a special diet. We will draw blood from your arm once a year at each yearly visit. Your urine will be checked very often, sometimes daily but at least weekly, for 5 years using a urine testing kit that can be used at home.

Your mom or dad will say if it is okay for you to be in this study. You can ask us any questions about the study that you want at any time.

Print participant's name: _____