Addi and Cassi's Hydroxy-Propyl-Beta-Cyclodextrin Compassionate Use Clinical Study

Protocol Extension 1.0

July 7, 2009

Sponsor: Caroline Hastings, M.D.

Study Site: Renown Hospital, Reno, Nevada

Patients: Addi and Cassi Hempel

IND #: **104,114 (Addison Hempel) and 104,116 (Cassidy Hempel)**

Addi and Cassi Hempel (DOB 1/23/2004), identical twin Caucasian females, received a definitive diagnosis of Niemann Pick Type C in October, 2007. The girls have been receiving miglustat (Zavesca®) 100 mg BID for almost one year. In addition, the children are receiving nutritional supplements including Curcumin.

Both children have been participating in a study at the National Institutes of Health designed to track the progression of Niemann Pick Type C disease. The children were last examined at the NIH in July of 2008. Both children continue to exhibit hepatosplenomegaly and clinical deterioration consistent with disease progression as manifested by severe neurological symptoms including cerebellar ataxia, dysarthria, dysphagia, vertical supranuclear palsy and cataplexy as well as progressive dementia.

On April 13, 2009 under the above compassionate use INDs the children began receiving intravenous infusions of hydroxyl-propyl-beta-cyclodextrin (HPBCD) starting at a dose of 80 mg/kg/day. The dose of HPBCD has been escalated on a monthly basis to current levels of 400 mg/kg/day administered as a weekly eight hour infusion in a hospital setting.

Because the treatment has failed to result in significant observable clinical improvement or in adverse events, increased dosing frequency (twice/week) and rate of dose titration (100 mg/kg/infusion) will be increased starting July 16, 2009.

Attached is the proposed treatment plan for the next 12 weeks is as follows:

	Baseline* Week 13 core protocol	Week 1	Week 2	Week 3	Subsequent Weeks 4- 12	Discontinuation Week 13
Dose Escalation. Following normalization of AST, dose will be held constant for subsequent infusions.		500 mg/kg/d; 8 hrs x1 + 3-4 days 600 mg/kg/d; 8 hrs x1	700 mg/kg/d; 8 hrs x1 + 3-4 days 800 mg/kg/d; 8 hrs x1	900 mg/kg/d; 8 hrs x1 + 3-4 days 1000 mg/kg/d; 8 hrs x1	Add 100 mg/kg/d; 8hrs Every 3-4 days	
Physical exam	X	X	X	X	X	
Neurological exam	X	X	X	X	X	
Volumetric CT						X
Renal Function (GFR)						X
Vital sign	X	Q 15 min x 4 + Q 30 min x 2 + Q 240 min x 5	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	
Renal labs[1]	X	X	X	X	X	
Hematology[2]	X	X	X	X	X	
Chemistry[3]	X	X	X	X	X	
Biomarker sample (15 ml whole blood)	X	X	X	X	X	
Urinary cholesterol sample 10 ml	X	X	X	X	X	

[1] Serum BUN/Cr; am spot urine Pr/Cr; UA

[2]CBC with Platelets, lipid panel

[3]Amylases, AST, ALT, bilirubin

*Baseline values can be used from Week 13 of the core protocol.

- **Baseline Clinical Assessment.** Prior to the initiation of HPBCD infusion both children will have the following assessments performed:
    - Complete physical and neurological exam which will be videotaped
    - Complete blood chemistry
    - Renal function test
    - Urinalysis
    - Volumetric CT of liver and spleen
    - A 15 ml blood sample and 10 ml urine sample will be retained for experimental purposes related to biomarkers and urinary cholesterol determinations.

- **Initial infusion.** Both children will continue to receive infusions of HPBCD in the pediatric ward at Renown Medical center hospital in Reno, NV a facility equipped with a pediatric ICU. Dosage will be increased by 100 mg/kg/ day from the previous level and will be infused over 8 hours at a rate of 20 ml/hr. The initial infusion will be **500 mg/kg/day**. The solution will be administered as prepared in sterile water for injection. The final concentration will be precise based upon the weight of the patients.

  The solutions will be prepared by a pharmacy certified by the Nevada Board of Pharmacy to prepare Compounded Sterile Products in accordance with current USP chapter 797 guidelines for aseptic processing. Specifically, for a high-risk non-sterile material received in bulk the following procedure will be employed:
    - In a ISO class 5 or cleaner room the HPBCD will be weighed and dissolved in 500 ml of sterile water using sterile containers.
    - Terminal sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.22-µm porosity filter entirely within an ISO Class 5 or superior air quality environment.
    - The sterilized solution will be placed into commercial infusion bags, under ISO class 5 or cleaner conditions, and labeled according to the pharmacy SOP with before use dating of 24 hrs in accordance with USP 797*: "For a sterilized high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature."*
    - The solutions will be delivered to the clinic no more than 4 hours prior to use.

- **Safety Monitoring.** Vital signs will be monitored every 15 minutes for the first hour during initiation of IV infusion, every 30 minutes during the second hour, and then every four hours. At the conclusion of the HPBCD infusion, and prior to any subsequent infusions, the patients will receive complete blood chemistry and urinalysis. In the unlikely event that a severe allergic reaction should occur, the following specific plan to deal with the possibility of anaphylactic or hyper-allergic response will be in place:

  A standard cardex for each patient in the clinic is prepared. This card (bright orange and on top of the clinic chart at each visit) has the name, age and weight of the child. The standard drugs for resuscitation in the event of allergy or anaphylaxis are on the chart and the doses are pre-calculated. We then arrange to have these drugs available in the clinic or hospital room, at the bedside, and draw them if needed prior to administration. The protocol for initial management includes:

- Discontinue the drug.
- Establish airway if necessary. Assess breathing; Supply with 100% oxygen with respiratory support as needed. Assess circulation and establish IV access. Place patient on a cardiac monitor.
- Albuterol nebulized, 0.05 to 0.15 mg/kg in 3 ml NS every 15 minutes as necessary.
- Diphenhydramine 1mg/kg IV or IM
- Methylprednisolone 2 mg/kg IV

- If patient is hypotensive:
- Place in Trendelenburg position, head at 30-degree angle below feet.
- IV fluid bolus, NS or LR 20 ml/kg IV over 5 to 15 minutes. Repeat as necessary.
- Epinephrine 1:10,000, 0.01 mg/kg (0.1 cc/kg) SC or IV.

In the event any symptoms of allergy or anaphylaxis occur, the patient will be admitted to the PICU for observation and further management.

- **Subsequent infusions.** Assuming the previous HPBCD infusion occurs without adverse events, the patients will receive additional 8 hour infusions every three to four days (i.e., twice/week). Dosage of all subsequent infusions will increase by 100 mg/kg/day until either liver transaminase return to normal levels or signs of toxicity are observed. Following normalization of transaminase levels, dosage will be held constant for subsequent infusions. The patients will have vital signs (e.g., heart rate, blood pressure, temperature) monitored as above during the infusions, and will undergo a physical examination, including neurological assessment, and clinical laboratory measurement weekly.

- **Dosage adjustment.** In the absence of side effects or adverse events (defined as serum creatinine greater than or equal to 2.5 times baseline values or worsening of liver transaminase (AST and ALT) greater than 3 time baseline dosage will continue to be increased. If laboratory values should be elevated above the limits, the drug will be discontinued until they return to acceptable levels. The drug may then be re-started at a dose of 100 mg/kg/day less than the most recent dose.

- **Study termination.** In the event clinically significant adverse events are observed, the study may be terminated at any time at the discretion of the investigator. Throughout the study stopping criteria will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v3) Grade 4 toxicity. At the end of three months treatment the data will be reviewed with the FDA and a decision whether to continue treatment will be made.

- **Therapeutic endpoints.** The primary endpoint of this study continuation will be improvement liver transaminase (AST consistently 2x normal in both patients as a concomitant of NPC disease) and in neurological functioning. Secondarily, arrest of disease progression will be assessed based upon independent expert review of the case report and video assessments. At three month intervals and/or at the conclusion of the study a complete physical and videotaped neurological exam will be performed. Changes in neurological status will be assessed using independent ratings of the videotapes examined by a pediatric neurologist. A volumetric CT of the liver and spleen will obtained for possible changes in hepatosplenomegaly. Following each infusion a 15 ml blood sample and 10 ml urine sample will be retained for experimental purposes related to biomarkers

and urinary cholesterol determinations as reflected in the sample collection protocol below. Weekly assessment by the parents will examine quality of life measures and a global impression of change will be made.

- **Biomarkers.** Collection of biomarkers and pharmacokinetic samples will be performed using baseline specimen collections and at eight week intervals. Additional samples will be collected at study conclusion.

  For pharmacokinetic estimates, samples will be obtained from the MediPort at baseline, and via venipuncture at 1-2 hours after the start of the infusion, and at 10-15 minutes post infusion.

###