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January 21, 2009

**RE: IND 104,116 CLINICAL HOLD COMPLETE RESPONSE**

Dear Dr. He:

Thank you for your letter concerning this compassionate use IND, and for your helpful suggestions. While we are distressed about the clinical hold given the dire circumstances facing Addi and Cassi Hempel, we are confident that this complete response to the concerns expressed in your letter will be adequate to permit moving forward in a timely manner with the revised treatment plan (enclosed).

To address the specific deficiencies and the information needed to resolve these issues:

- 1. There is no information regarding the concentration of the solution that will be prepared by the pharmacist. Also, it is not clear whether the solution will be administered as prepared or as an admixture with commercial diluents. You must provide the information regarding the concentration of the solution that will be prepared by the pharmacist and clarify if the solution will be administered as prepared, or as an admixture with commercial diluents.*

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. As proposed in the revised treatment plan a 20 mg/kg/hr dose of HPBCD at a rate of 20 ml/hr would translate for an approximate 20-25 kg patient to a final concentration of about 20-22 mg/ml.

2. *There are no details regarding procedures that will be used to assure sterility of the infusion solution (e.g., will it be aseptically filtered?). You must provide details regarding the procedures that will be used to assure sterility of the infusion solution.*

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- $\mu$ m 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.”*

3. *There is no information regarding how long the solution will be stored (and under what conditions) before administration. You must clarify how long the solution will be stored, and what conditions it will be stored under, prior to administration. Assurance will need to be provided that the drug substance is stable in solution during storage and during the four day infusion period.*

The solution will be prepared on a daily basis no more than four hours prior to use. The product is highly soluble (more than 3000 mg/ml in water at room temperature). Concerning stability of HPBCD solutions, literature values <http://www.researchd.com/janssen/410200.htm> indicate "HPBCD was incubated in buffers at 50 degrees C for 5 days. The results indicated that little, if any hydrolysis occurred. Variation in the assay could account for the differences found." While no specific stability data exists on the proposed solutions, no stability problems are anticipated given the literature documentation and daily preparation of the solution.

4. *Insufficient data exists to determine if the doses to be administered to this patient are safe. The available published studies are not adequate to assess the safety of your proposed dose. Available pre-clinical data suggest that the proposed IV dosing would pose a significant risk of renal toxicity as well as possible toxicity to other organs (e.g., liver, lung, and pancreas). This is true regarding the initial proposed four day IV infusion, subsequent weekly eight hour infusions, and monthly infusions with possible dosing increments of 40 mg/kg/hr. Six months of chronic toxicity studies with HPBCD in a rodent and non-rodent species is required to determine the appropriate starting dose for the proposed study subjects.*

We disagree with the Division's position on this point for several reasons:

- While both beta-cyclodextrin and tri-methyl-cyclodextrins are relatively toxic due to their lower aqueous solubility, the addition of the hydroxyl-propyl moiety to beta cyclodextrin appears to greatly reduce this toxicity. In fact, Brewster et al (Int. J. Pharmaceutics, 59: 231-243, 1990) have administered up to 10 grams/kg by IV infusion to monkeys without toxicity. These authors also conducted subchronic IV studies in rats and monkeys of 200 mg/kg administered every second day for 13 weeks without toxicity. The authors concluded that **"based on work presented here and elsewhere, the toxicity of HPCD is approaching that of glucose."**
- The dose regimen proposed has been used previously (described by Carpenter et.al. . (J. Pediatrics, 1987, pp507-512) at 20 mg/kg/hr x 4 days) without toxicity.

- An FDA approved antifungal has previously been administered to children in 100 mg/kg HPBCD as a 1 hr intravenous infusion, which is one fifth the dose proposed in this study.
- Sign of renal and other toxicities will be monitored closely during the study (see #5 below).
- We concur with the Division that subsequent dose increments increased by 40 mg/kg/hr might be excessive. The intent was to increase the HPBCD if and only if the initial four day infusions were well tolerated. Because there are two twins in the study the idea was to randomize the patients to initially receive 20 or 40 mg/kg/hr x 8 hrs. If well tolerated, each patient would have their subsequent dose increased weekly until signs of toxicity were observed, then the dose would be scaled back. We propose that the weekly increments by 20 mg/kg/hr and the protocol has been modified to clarify this issue.
- The requirement for six month chronic toxicity studies is unfeasible given a) the non-commercial nature on this IND; b) the expense burden to the family that this requirement would inflict; and c) there is no assurance that the children will be suitable candidates for the treatment in the time it would take to complete such studies.

If the Division has persistent concerns about the safety of the proposed dosing regimen, or is aware of specific toxicity issues based upon other INDs, we would welcome a suggestion for a different starting dose and escalation algorithm based upon safety manifested by clinical laboratory results.

5. *The protocol lacks sufficient detail regarding safety monitoring. Clarify the safety monitoring protocol to be followed (frequency of vital sign monitoring) during and after infusion. We recommend that you monitor vital signs every 15 minutes for the first hour during initiation of IV infusion, every 30 minutes during the second hour, and then every four hours.*

We agree with the Division on the necessity for frequent safety monitoring. This is one of the reasons that the initial four day infusion will be performed in a hospital setting with a pediatric ICU. We have revised the protocol to include the Division's suggested monitoring frequency.

6. *There is no plan provided for management of an anaphylactic response. Please provide details regarding how a hyper-allergic or anaphylactic response will be managed to ensure the patient's safety in a monitoring setting.*

Again, the fact that the study will be performed in a hospital setting well equipped to deal with unexpected adverse events should mitigate the Divisions concerns. Furthermore, the following specific plan to deal with the possibility of anaphylactic or hyper-allergic response has been incorporated into the study plan:

We have a standard cardex for each patient in the clinic. 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.

7. *The protocol does not adequately describe the schedule of clinical evaluations after the initial four day infusion. Please revise the protocol to state that patients will have vital signs (e.g., heart rate, blood pressure, temperature) monitored, and will undergo a physical examination, including neurological assessment, weekly for the first three months, and then every month.*

The Division's suggestion has been incorporated into the revised protocol.

8. *The protocol does not define adequate criteria for terminating the study. Please define stopping criteria in the study protocol based on, for example, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v3) Grade 4 or 5 toxicity events, or propose alternate stop criteria that are consistent with safety events of concern in this study.*

The Division's suggestion has been incorporated into the revised protocol.

Non-hold issues to be addressed:

9. *Please report all adverse events in accordance with grading system for adverse events as the NCI criteria.*

Agreed.

10. *The protocol lacks a clear statement of the objectives and the study endpoints. Please clarify your study objectives and endpoints.*

It is quite difficult to define with the usual clarity and precision what the appropriate endpoints should be in this study. In the "best case" we would hope for some restoration of neurological functioning (e.g., return of some language skills). A "good" clinical outcome would be to arrest disease progression and prolong life expectancy, which would likely be difficult to

assess over the short term. Tertiary outcomes that will be assessed include reduction in liver or spleen volumes, increased urinary excretion of cholesterol, or other “benefits” observed by the parents. The revised protocol attempts to address these issues.

*11. Please clarify the timing of doses and the overall study duration.*

We propose that the study be of six month duration. If at the end of the six month period there appears to be therapeutic benefit, a protocol extension will be submitted to the IND along with a progress report. Following the initial four day infusion, it is the intent of the study as described in the protocol to administer weekly 8 hour infusions for the duration of the study.

*12. Please provide a copy of the Informed Consent Form you intend to use.*

The currently proposed Informed Consent Form is being reviewed by the IRB. The final approved form will be submitted to the IND as requested.

*13. Please provide a copy of the Case Report Form (CRF) you intend to use.*

Any Case Report Forms used beyond the standard chart records of neurological and physical exams, safety vital signs, clinical lab reports, renal function test results, and volumetric CTs will be submitted to the IND.

Dr. He, we believe that the above additional information and clarifications should address adequately the concerns expressed in your letter. Given the severity of Niemann Pick Type C disease and the rapid neurological deterioration manifested in the children covered by this compassionate use IND (e.g., loss of verbal ability), we feel it is vitally urgent to initiate the proposed treatment plan as promptly as is reasonably safe given the absence of any treatment alternatives. It is our hope that the results of this study will also benefit other children with NPC disease. Be assured that regardless of the treatment outcome, this study will receive significant media coverage and awareness in the NPC community.

We believe that the above issues require urgent attention, and we will immediately request a Type A meeting under separate submission along with the appropriate documentation.

Sincerely,  
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CC: Christi Stark, Regulatory Project Manager with enclosures

Enclosures: Triplicate copies: this cover letter, FDA 1571, Revised Protocol