July 7, 2009

Ruyi He, M.D.
Acting Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Dear Dr. He:

We anticipate completing the dose escalation protocol on July 9, 2009 with the fourth infusion of hydroxyl-propyl-beta-cyclodextrin (HPBCD) at a dose of 400 mg/kg/day administered over an eight hour period. To date, we have not observed any remarkable clinical changes or any adverse events. This is likely due to the conservative, insufficient dosing schedule employed. Nevertheless, the parents are convinced that the HPBCD infusions are providing some benefit to their children as manifested by better muscle control and the appearance of increased general well being. We propose to continue dose escalation as per the enclosed protocol extension.

Recent pre-clinical studies have consistently demonstrated one major effect of HPBCD in both mouse and cat models of Neimann Pick Type C disease (NPC). That is, a normalization of liver transaminase enzymes which are typically elevated in these animals as well as humans (see Liu et al paper, enclosed). In fact, at a dose of 1000 mg/kg/week in cats, ALT and AST are normalized in the absence of increased longevity or changes in neurological symptoms. Ongoing studies in cats (C. Vite, APMRF conference, May 2009) at 4000 and 8000 mg/kg/week appear to be delaying the onset of neurological symptoms and to be normalizing ALT and AST. As summarized below, we have failed to see significant changes in these enzymes in AH and CH, arguably due to insufficient dosing. However, a trend in lowering cholesterol seems to have occurred following the four day continuous infusion, returning during the intermediate dose period, and beginning to lower again at the maximum 400 mg/kg/day. We propose to monitor closely these markers in the protocol extension phase of the study.

ALT, AST, Cholesterol summary

	Reference	Baseline	Week1 Day 5	Week2	Week3	Week4	Week5	Week6	Week7
Date:	**07/02/2009**	**04/07/09**	**4/17/09**	**4/23/09**	**4/30/09**	**5/07/09**	**5/14/09**	**5/21/09**	**5/28/09**
Dose (mg/kg/day) 1x/week except week 1	**xx**	**xx**	**80 x4**	**160**	**160**	**160**	**160**	**320**	**320**
AH ALT	2-50	13	14	17	13	19	17	17	31
AH AST	12-45	**74**	**66**	**79**	**75**	**93**	**83**	**86**	**87**
AH Cholesterol	131-197	154	103	133	130	131	106	120	148
CH ALT	2-50	13	17	30	20	24	11	14	20
CH AST	12-45	**80**	**91**	**93**	**88**	**88**	**89**	**95**	**93**
CH Cholesterol	131-197	141	133	123	126	131	116	126	163
	Reference	**Week8**	**Week9**	**Week10**	**Week11**	**Week12**	**Week13**	**END**	
Date:	**xx**	**6/4/09**	**6/11/09**	**6/18/09**	**6/25/09**	**7/2/09**	**7/9/09**	**7/10/09**	
Dose (mg/kg/day)	**xx**	**320**	**320**	**400**	**400**	**400**	**400**		
AH ALT	2-50	44	37	17	15	18			
AH AST	12-45	**97**	**85**	**74**	**74**	80			
AH Cholesterol	131-197	168	152	129	120	129			
CH ALT	2-50	22	19	11	12	20			
CH AST	12-45	**96**	**91**	**72**	77	84			
CH Cholesterol	131-197	151	131	113	112	125			

Recently, we became aware of an unpublished summary from toxpath.org of toxicology studies conducted in rats and dogs with cyclodextrins. We are enclosing a copy for reference.

While we have not been able to collect directly pharmacokinetic data on HPBCD in these patients, we have modeled the theoretical profile (enclosed). From this model data it is illustrative that the exposure levels experienced by AH and CH are far below that proposed in our original submission (480 mg/kg/day x 4 days as 20 mg/kg/hrx96 hrs). We believe that in order to achieve any significant effect from HPBCD much greater concentrations (or duration of infusion) will be required. Given the stress to the children of the hospitalization required for the infusions, and the significant financial burden to the

parents, we believe strongly that a more rapid dose escalation is warranted. We propose starting a twice weekly infusion and to escalate the dose by 100/mg/kg/infusion until either normalization of AST or signs of toxicity are observed.

Sincerely,
Caroline Hastings, M.D.
Director, Fellowship Program
Children's Hospital & Research Center Oakland
747 52nd Street
Oakland, CA 94609-1809

CC: Christi Stark
Stacy Barley with enclosures

Enclosures: (triplicate copies of each of the following documents)

- This cover letter
- FDA 1571
- Liu et al PNAS paper
- Rat and dog toxicity report
- Pharmacokinetic estimates 6/18/09
- Protocol Extension 1.0