Phase 1/2a study of 2-Hydroxypropyl-β-Cyclodextrin Therapy for Infantile Liver Disease Associated with Niemann-Pick Disease, type C

NCT03471143

11-13-2024

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Study type (check all that apply):
___X___Archived biological specimens/medical information

_____Natural history; definition of phenotype, genotype/phenotype correlation
_____Prospective linkage/gene identification, NOT providing information to participants
_____Prospective linkage/gene identification, providing information to participants
_____Social science; assessments of knowledge, attitudes and behavior
___X___Drugs or devices
_____Gene transfer
_____Other interventions

Estimated Duration of study: Four Years

Subjects: 12 subjects, 0-1 years of age

Ionizing radiation: Medically indicated

Research participants to be seen at:
_____NIH only*
___X___Off-site only
_____Both NIH* and off-site
Includes participants who physically come to the NIH Clinical Center and/or for whom specimens/data are analyzed by Clinical Center departments. If participants will be seen at NIH, a Medical Advisory Investigator must be indicated on the 1195 form, unless this is a social science project with no clinical interventions.

Collaborative Project:

National Institutes of Health	FWA00005897
Washington University	FWA00002284

Identifying words:

Niemann-Pick Disease, type C1, Neurodegenerative, Lysosomal Storage
2-hydroxypropyl-β-cyclodextrin, Phase 1/2a

IND Sponsor: **Patricia I. Dickson, MD**

Protocol version: **11-13-24, Amendment 10**

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Abbreviations

Abbreviations	Description of Abbreviations
24-OHC	24-(S) hydroxycholesterol
27-OHC	27-hydroxycholesterol
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUA	American Urological Association
AUC	Area under the curve
AUC_{0-t}	Area under the plasma or CSF concentration-time curve from zero (0) hours to time (t)
Caregiver-CGIC	Caregiver-Clinical Global Impression of Change
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
Clinician-CGIC	Clinician-Clinical Global Impression of Change
Cmax	Maximum plasma concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSS	Clinical Severity Score
CT	Cholestane-3β,5α,6β-triol
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPOAE	Distortion Product Otoacoustic Emission(s)
DSC	Dose Selection Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCA	Glycine-conjugated trihydroxycholanic acid or Glycine Conjugated Acids
GLP	Good Laboratory Practice
GRAS	Generally regarded as safe
HPBCD	2-hydroxypropyl-β-cyclodextrin
hsCRP	C-Reactive Protein High Sensitivity
IC	Intracisternal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICV	Intracerebroventricularly
IEC	Independent Ethics Committee
iIND	Investigator Sponsored Investigational New Drug Application
IND	Investigational New Drug Application
IRB	Institutional Review Board
IT	Intrathecal
IUD	Intrauterine device
IV	Intravenous

Abbreviations	Description of Abbreviations
LE/LY	Late endosomal/lysosomal
LGAL3	Galectin 3
Lipid-509	LysoSM-509
LP	Lumbar puncture
LSOs	Lysosomal storage organelles
mITT	Modified intent-to-treat
NCI	National Cancer Institute
NfL	Neurofilament light chain
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NOAEL	No observable adverse effect level
NPC	Niemann-Pick disease, type C
NPC/Npc1 and NPC2	Genes that, when mutated, cause NPC phenotypes
NPC1	Niemann-Pick disease, type C1 phenotype
NPC1	Niemann-Pick disease, type C1 cat phenotype
Npc1 or Npc1$^{-/-}$	Niemann-Pick disease, type C1 mouse phenotype
OAE	Otoacoustic emissions
PPCS	N-palmitoyl-O-phosphocholineserine
PT	Prothrombin time
PTA	Pure Tone Audiometry
QoL	Quality of life
SAE	Serious adverse event
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SE	Standard error
SOP	Standard operating procedure
SPL	Sound pressure level
SUSAR	Serious and unexpected suspected adverse reaction
TUG	Timed up and go
ULN	Upper Limit of Normal
US	United States
$V_{d,ss}$	Volume of distribution at steady-state
VSNGP	Vertical supranuclear gaze palsy

1. Précis

Niemann-Pick disease type C (NPC) is a lethal, autosomal recessive, lysosomal storage disorder characterized by neurodegeneration in early childhood and death in adolescence. NPC results from mutation of either the *NPC1* (~95% of cases) or *NPC2* genes. Biochemically, NPC is characterized by the endolysosomal storage of unesterified cholesterol and lipids in both the central nervous system and peripheral tissues such as the liver. Individuals with NPC demonstrate progressive cerebellar ataxia and dementia. Acute cholestatic liver disease is frequently observed in the neonatal/infantile period but subsequently resolves. However, chronic, sub-clinical liver disease persists. Intrathecal 2-hydroxypropyl-β-cyclodextrin (HPBCD), also known as adrabetadex () has proven effective in reducing signs and prolonging life in NPC1 animal models, and Phase 1/2a data support efficacy in NPC1 patients. Adrabetadex has also been shown to be effective in treating liver disease in the NPC1 cat.

This Phase 1/2a, open-label, multiple ascending dose, multi-center trial will evaluate whether Adrabetadex administered intravenously is effective in treating acute liver disease in NPC infants. The objective of this study is to determine the safety, tolerability and efficacy of intravenous adrabetadex in NPC disease. The primary endpoint is the efficacy of adrabetadex to reduce plasma levels of glycine-conjugated trihydroxycholanic acid ("bile acid biomarker"), an NPC-specific pharmacodynamic biomarker. Secondary endpoints are assessment of the dose-response relationship for attenuation of liver dysfunction, as determined by reduction in serum transaminases (ALT and AST) and liver size. Exploratory lipid, protein, and inflammatory biomarkers will also be examined. This study will enroll up to 12 subjects (6 subjects per dose level) and evaluate two dose levels (500 and 1000 mg/kg). In the first phase of the study, drug will be administered twice a week for six weeks for a total of 12 administrations. Subjects who demonstrate either a significant reduction in the glycine-conjugated trihydroxycholanic acid biomarker or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) will be allowed to crossover into a second open-label phase. In this phase of the study, drug will be administered monthly for six months for a total of six administrations. Serum transaminases (ALT and AST) and an abdominal ultrasound will be obtained at the end of the 6-month open-label extension phase. Efficacy will be assessed by reduction in serum transaminases and reduction in spleen volumes. NPC biomarkers [(cholestane-3β,5α,6β-triol (CT), glycine-conjugated trihydroxycholanic acid (GCA),phosphocholinerase (PPCS)/lysoSM-509 (Lipid-509), 24(S)-hydroxycholesterol (24-OHC), 27-hydroxycholesterol (27-OHC), and neurofilament light chain (nfL)] will also be obtained at these time points and will be considered exploratory outcome measures.

2. Introduction

2.1 Niemann-Pick Disease, type C1

Niemann-Pick disease, type C (NPC) is a recessive lysosomal storage disorder characterized by impaired intracellular trafficking and subsequent endolysosomal accumulation of unesterified cholesterol and other lipids in the central nervous system and visceral organs (1). NPC results from mutation of either the *NPC1* or *NPC2* genes, with the vast majority (~95%) of cases due to impaired NPC1 function. Incidence of classical NPC has been estimated to be on the order of 1/89,000-104,000 with potential of a late-onset variant of NPC1 with incidence on the order of 1/36,000 (1, 2). The NPC1 phenotype is heterogeneous with respect to both age of onset and symptom complex. Visceral disease including hepatosplenomegaly and cholestatic jaundice of variable severity can be present in early childhood and is followed by progressive neurological disability (3, 4). Common neurological signs and symptoms include vertical supranuclear gaze palsy, cerebellar ataxia, gelastic cataplexy, seizures and cognitive impairment. An adult-onset variant with prominent psychiatric symptoms has recently been characterized (5). Diagnosis of NPC1 is frequently delayed, but the recent development of a serum-based diagnostic test will facilitate earlier diagnosis (6-8). There are no FDA approved therapies for NPC1, although miglustat (Zavesca®) has been approved for use in the European Union and multiple other countries (9-12) based on a controlled trial and long-term extension studies.

2.2 Liver Disease in Niemann-Pick Disease, type C1

In infantile and juvenile forms of the disease, patients frequently present with cholestasis or hepatosplenomegaly. NPC has been reported to be the second most common genetic metabolic disorder with neonatal liver disease (13), and was diagnosed in up to 8% of neonates presenting with intrahepatic cholestasis in one case series (14). In the majority of cases the liver disease becomes subacute, although in other cases the liver disease can progress to liver failure. In the majority of cases, liver inflammation and dysfunction persists, as evidenced by chronic elevations in serum transaminases and abnormal prothrombin (PT) and activated partial thromboplastin (PTT) times. Approximately two-thirds of NPC1 subjects enrolled in the NIH Natural History study (06-CH-0186) have had elevated serum transaminases. Liver disease in NPC can result in a lethal degree of hepatic fibrosis and the chronic disease predisposes to hepatocellular carcinoma (15-18). Although interim analysis of the Phase 1/2a trial data indicates that IT therapy has an impact in slowing neurological disease progression, direct CNS delivery, appears unlikely to have an effect on peripheral disease, based on liver chemistries. In the NPC1 cat model subcutaneous administration of HPBCD 1000 mg/kg biweekly (11 treatments over 21 weeks) reduced serum ALT from ~6-fold elevated to 2-fold elevated (19). This was accompanied by correction of the severe vacuolization of hepatocyte and Kupffer cell cytoplasm observed in untreated cats. In human NPC patients dosed under an individual IND, IV administration of HPBCD (2500 mg/kg biweekly) reduced by ~2-3-fold plasma concentrations of cholestane-3β,5α,6β-triol (20) and its metabolite, trihydroxycholanic acid glycine conjugate (21). Both cholesterol-derived metabolites are NPC disease-specific biomarkers that monitors oxidizable free cholesterol in liver tissue (7). A recently discovered NPC plasma biomarker, lipid-509 (22), has been evaluated in treatment settings.

Taken together, the preclinical and human data suggest that IV HPBCD may be effective in reducing liver inflammation and injury and may prevent the long-term sequelae, such as cirrhosis and risk of hepatocellular carcinoma.

2.3 Investigational Product Description

2-hydroxypropyl-β-cyclodextrin (HPBCD) is a cyclic polysaccharide that can be used to solubilize hydrophobic compounds such as cholesterol. The potential therapeutic efficacy of HPBCD was first investigated by Camargo et al (23) utilizing a NPC1 mouse model (24, 25), but only slight neurological efficacy was observed. Subsequent studies by Liu et al (26, 27) and Davidson et al (28) demonstrated delayed progression of neurological signs and death in *Npc1* mutant mice. Therapeutic efficacy has also been demonstrated in the feline NPC1 model (19). Only 0.3% of HPBCD crosses the blood-brain-barrier (29), thus necessitating the use of extremely high peripheral doses or direct intrathecal infusion to treat the neurologic signs and symptoms of the disease. A Phase 1/2a trial of intrathecal HPBCD conducted at the NIH Clinical Center and 18-month data suggest significant

stabilization of neurological disease progression Based on these data, a multicenter, multinational Phase 2b/3 trial of intrathecal HPBCD was initiated in the fall of 2015. With the development of a potentially effective therapy for the neurological aspects of NPC1, consideration needs to be given to the treatment of visceral issues.

HPBCD, a generally regarded as safe (GRAS) substance, is a membrane-impermeant cyclic oligosaccharide with a distinctive truncated cone configuration containing 7 cyclo-α-(1,4)-anhydrogl p=0.002 with hydroxypropyl groups randomly substituted onto the C2, C3 and C5 positions of the substitu s (Fig. 1). All HPBCD are amorphous mixtures of different isomers, characterized by the degree of substitution, which represents the average of substitution of the hydroxyl with propyl groups per HPBCD molecule. The active drug substance in adrabetadex is KLEPTOSE® HPB parenteral grade, which has an average degree of substitution of 4.34 or on a molar basis 0.63 ± 0.01.

Cyclodextrins, as well as HPBCDs in general, are used extensively to solubilize pharmaceuticals and various regulatory authorities have approved them as excipients. The therapeutic potential of 2-hydroxypropyl-β-cyclodextrin (HPBCD) was discovered when HPBCD, injected systemically to *Npc1*$^{-/-}$ mice beginning at either postnatal day 7 or 21 and continuing every other day, delayed onset of clinical symptoms, reduced intraneuronal cholesterol and glycosphingolipid storage, reduced markers of neurodegeneration, and increased animal survival (27, 28). HPBCD enters cells by the endocytic pathway and is delivered to the endolysosomal storage organelles where unesterified cholesterol accumulates in NPC deficiency. HPBCD replaces the function of NPC1 protein and promotes transport of the accumulated unesterified cholesterol to the endoplasmic reticulum for esterification by acetyl CoA cholesterol:acyl transferase and subsequent efflux (30, 31). While the precise mechanism of HPBCD action to bypass or replace NPC1 function is not yet defined, HPBCD normalizes intracellular cholesterol trafficking by binding the hydrophobic moieties of cholesterol and other lipids.

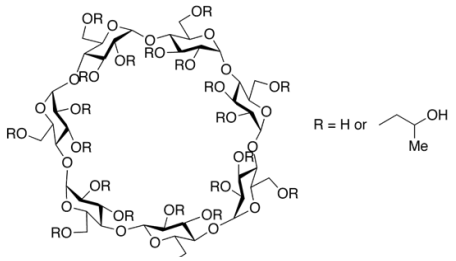

Figure 1. ADRABETADEX, HPBCD

2.3.1 Non-clinical Toxicology Studies

The pharmacological properties of HPBCD have been extensively studied in *Npc1*$^{-/-}$ mice and *NPC1* cats. The pharmacokinetic properties have been studied in rats, dogs, and the *Npc1*$^{-/-}$ mice and *NPC1* cats. The safety of HPBCD was evaluated in a comprehensive toxicology program conducted by Janssen Research Foundation (Janssen) to support its use as a pharmaceutical excipient. Preclinical toxicology studies included single and repeat-dose toxicity studies, in vitro and in vivo genotoxicity assays, carcinogenicity studies, reproductive and developmental toxicity (Segment I, II and III) studies and special toxicity (local tolerance and mechanistic toxicity) studies. HPBCDhas been approved for use as an excipient in oral and intravenous (IV) pharmaceuticals for over a decade. The Sponsor has obtained the rights to reference the Roquette Freres Type IV Drug Master File No. 9420 for HPBCD, the drug substance.

2.3.1.1 Acute Toxicity Studies

After a single IV dose of HPBCD mortality occurred in mice at a dose ≥ 10,000 mg/kg body weight. The most common clinical abnormality at all dose levels (5,000-20,000 mg/kg body weight) in mice was viscous urine. At lethal doses, typical signs of toxicity included soft feces, sedation, piloerection, clonic convulsions, dyspnea, hypothermia, loss of righting reflex, palpebral ptosis, and tremors. IV doses of 2,000 and 4,000 mg/kg body weight were not lethal in rats but did result in hyperemia. Rats in the 4,000 mg/kg body weight group also were observed with viscous urine, hypotonia, ataxia, and swelling of the ears, nose, and paws. Dogs survived single IV doses of 5,000 mg/kg body weight HPBCD. No clinical abnormalities were noted in the females, but coughing, diarrhea/soft feces, and emesis were observed in the males.

2.3.1.2 Repeat Dose Toxicity Studies

Repeat dose studies utilizing IV administration were performed in rats and dogs. Urinary tract changes were present after IV administration and included swollen and granular tubular cells in the kidney, swollen epithelial cells in the urinary bladder and renal pelvis, and vacuolated cortical tubules in the kidney. The no-observed-adverse-effect-levels (NOAELs) in the 3-month IV studies were 50 mg/kg body weight in the rat and 100 mg/kg body weight in the dog. In rats, higher doses (100 and 400 mg/kg body weight) led to reduced body weight gain. Hematological changes and altered serum chemistry were seen at the highest dose (400 mg/kg body weight). Urinary parameters were slightly modified and included increases in white blood cells, cylindrical epithelial cells, occult blood, and granular casts and decreases in specific gravity and creatinine associated with larger urine volume. Adrenal gland, spleen, and kidney weights were increased. Kidneys were pale at necropsy. Histological changes in the liver and lung included increased presence of Kupffer cells in the liver and foamy cells and white stipples in the lung. Following the 1, 2, or 3 months of recovery, most of these changes reverted to normal. After 3 months of recovery, the only remaining abnormalities were slightly elevated liver transaminases (400 mg/kg body weight), pale kidney (100 and 400 mg/kg body weight), swollen epithelial cells in the urinary bladder and pelvic epithelium (all doses levels). The corticotubular changes resolved completely (25 mg/kg body weight), almost completely (50 mg/kg body weight), or were partially reversible (100 and 400 mg/kg body weight). In dogs, IV administration of 400 mg/kg body weight, HPBCD led to transient soft feces and slightly elevated alanine aminotransferase (ALT) and bilirubin or haptoglobin. Macroscopic and microscopic (foamy cells) lung changes were seen as well. All of these changes resolved after 1 month of recovery. At the end of the 3-month recovery, swollen epithelial cells were still present in the urinary bladder and renal pelvis but vacuolated cortical tubules (with swollen lysosomes) were no longer present. Repeat-dose studies extracted from the literature also support these findings (32).

2.3.1.3 Reproductive and Developmental Toxicity Studies

Reproductive function (fertility) was not adversely affected by IV administration of HPBCD in rats. Maternal and paternal toxicity was limited to a slight reduction in body weight. No primary embryo toxicity was noted following IV administration in rats or rabbits. Associated with maternal toxicity, decreased survival and reduced birth weight and body weight evolution of the rat pups were noted at 400 mg/kg/day.. In a 2nd un-dosed generation, all variables were normal. No developmental toxicity was noted in any study.

2.3.1.4 Genotoxicity and Mutagenicity

The genotoxic potential of HPBCD was investigated in Ames tests (S. typhimurium and E. coli), a mammalian cell assay, chromosome aberration test, micronucleus tests, and deoxyribonucleic acid (DNA) repair tests. No mutagenic potential was evident in any of these studies.

2.3.2 Previous Human Experience with Intravenous HPBCD

Initial human experience with IV HPBCD derived from NPC1 patients who were dosed with IV HPBCD supplied by Johnson and Johnson in attempt to treat the CNS disease, despite its poor penetrance across the blood brain barrier. In the USA the investigators were aware of eight such patients receiving IV HPBCD under expanded use INDs as of 2017. Doses up to 2500 mg/kg were infused over eight hours (312.5 mg/kg/hr) twice per week. Matsuo et al (33) reported on two NPC1 subjects who were given up to 2000 or 2500 mg/kg two or three times per week. In one subject dosed with 2500 mg/kg, transient diffuse pulmonary cloudiness and fever were reported in the context of an aspiration pneumonia and mechanical ventilation. However, decreased liver size and AST levels (from 3.5-fold elevated to 2-fold elevated) were observed in this same subject after 3-4 months of therapy. In a second subject, there were no changes in liver size although AST levels were slightly reduced (1.2-fold elevated to normal range).

IV HPBCD is currently under investigation by Cyclo Therapeutics, NCT04860960. To the best of our knowledge, as far as we are aware, no serious adverse events have been reported. As of August 2023, Dr. Berry-Kravis is aware of 19 patients treated with IV HPBCD under an expanded access program.

2.3.3 Previous Human Experience with Intrathecal HPBCD

In addition to IV administration of HPBCD, NPC1 patients and study participants have received intrathecal (IT) HPBCD (i.e., delivered into the cerebrospinal fluid). The results of a sham-controlled 1-year study (parts A and B) of up to 1800 mg IT adrabetadex delivered every 2 weeks were announced in 2018 and reported on clinicaltrials.gov. In that study, there was no separation between the treated and sham groups in the coprimary outcomes: the NPC-CSS scale 4 key domains and the CGIC. There were no substantial or significant differences between treatment and sham groups with respect to treatment-emergent adverse events, with the exception of hearing loss, which is an expected AE with IT dosing of HPBCD.

2.4 Study Rationale

As described earlier (section 2.2), NPC1 subjects frequently present with acute cholestatic liver disease in the newborn period. In the majority of cases the liver disease becomes subacute, although in other cases the liver disease can progress to liver failure. The goal of this therapy is to reduce the risk of progressive hepatic damage that results in hepatic fibrosis and need for liver transplantation.

2.5 Route of Administration and Dose Selection Rationale

In the NPC1 cat model, subcutaneous administration of HPBCD 1000 mg/kg biweekly (11 treatments over 21 weeks) reduced serum ALT from approximately 6-fold elevated to 2-fold elevated (19). This was accompanied by correction of the severe vacuolization of hepatocyte and Kupffer cell cytoplasm observed in untreated cats.

In two US NPC1 patients dosed under an individual IND, intravenous (IV) administration of HPBCD (2500 mg/kg biweekly) reduced by 2-fold plasma cholestane-3β,5α,6β-triol (20), an NPC1 disease-specific biomarker that monitors oxidizable free cholesterol in liver tissue (7). Liver volume and AST were reduced in one of two subjects in Japan treated with 2500 mg/kg (33). Toxicity appears to be limited. One of two subjects treated demonstrated pulmonary infiltrates at 2500 mg/kg, though this occurred in the context of an aspiration pneumonia and mechanical ventilation (33). The precise duration of the pulmonary infiltrates was not reported, though the aspiration pneumonia resolved after three weeks. IV HPBCD has been used under an emergency IND for acute liver failure in NPC1 neonates (see section 2.3.2).

Doses up to 1000 mg/kg have been administered to neonatal subjects < 2 months of age in the US. A 5-week-old NPC1 subject received 12 doses of adrabetadex, ranging from 250 mg/kg to 1000 mg/kg, over a 6-week treatment period under an emergency IND (Sponsor: Marwan Shinawi MD). The NPC biomarker, lipid-509, declined from a pre-treatment value of 3240 ng/ml to 1610 ng/ml after 10 doses, consistent with reduction of liver lipid storage. Additionally, a 3-week old NPC1 subject received 12 doses, ranging from 250 mg/kg to 500 mg/kg, over a 6-week period under an expanded access protocol (Sponsor: Amarilis Sanchez-Valle). The treatment was accompanied by a reduction in glycine-conjugated trihydroxycholanic acid (“bile acid biomarker”) from 16 ng/ml pre-treatment to 11.1 ng/ml at the end of 6 weeks (12 doses). In both NPC1 neonates, all the adrabetadex doses were well tolerated without adverse effects. Right of reference was provided by both Sponsors.

Taken together, the preclinical and human data suggest that adrabetadex administered by the IV route may be effective in reducing liver inflammation and injury and may prevent the severe long-term sequellae, such as hepatic fibrosis, hepatocellular carcinoma, and liver failure that requires transplantation. The safety, tolerability, and clinical efficacy of the drug will be determined in this dose-finding study.

3. Study Objectives

The overall goal of this study is to reduce the risk of progressive hepatic fibrosis due to inflammation in infants with Niemann-Pick Disease, type C. The objectives of this study are to determine the safety, tolerability and efficacy of intravenous adrabetadex in NPC disease following 12 doses given twice weekly for 6 weeks. The primary endpoint is the efficacy of adrabetadex to reduce plasma levels of glycine-conjugated trihydroxycholanic acid ("bile acid biomarker"), an NPC-specific pharmacodynamic biomarker. Secondary endpoints are assessment of the dose-response relationship for attenuation of liver dysfunction, as determined by reduction in serum transaminases (ALT and AST) and liver size. Exploratory lipid, protein and inflammatory biomarkers will also be examined. Subjects who demonstrate significant reduction either in the glycine-conjugated trihydroxycholanic acid biomarker or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) will be allowed to crossover into the second phase of the study, an open-label phase of six months duration in which IV adrabetadex will be administered monthly for a total of six doses. Serum transaminases (ALT and AST) and an abdominal ultrasound will be obtained at the end of the six-month open-label extension phase. Efficacy will be assessed by reduction in serum transaminases and reduction in spleen volumes. NPC biomarkers (cholestane-3β,5α,6β-triol, glycine-conjugated trihydroxycholanic acid,PPCS/lipid-509, 24(S)-hydroxycholesterol, 27-hydroxycholesterol, and neurofilament light chain) will also be obtained at these time points and will be considered exploratory outcome measures.

4. Specific Aims

Aim 1. To conduct a Phase 1/2a, open-label, multi-center, multiple ascending dose study of intravenous adrabetadex to evaluate the safety and tolerability in treating cholestatic liver disease in infants with NPC1

Aim 2. To evaluate the efficacy of intravenous adrabetadex to reduce plasma levels of an NPC bile acid biomarker
(glycine-conjugated trihydroxycholanic acid)

Aim 3. To evaluate the dose-response relationship for adrabetadex to attenuate liver dysfunction, as determined by reduction in serum transaminases and liver size and exploratory research outcome measures (e.g., NPC1 disease and inflammatory biomarkers)

5. Study Design and Methods

5.1 Study Overview

The trial will be a Phase 1/2a, open-label, dose-escalation, multi-center study of adrabetadex in subjects with NPC dosed twice a week with IV adrabetadex for six weeks for a total of 12 administrations, followed by a six month open-label extension phase in which the subjects are dosed monthly with IV adrabetadex for six months for a total of six administrations. The study will characterize the safety, tolerability, preliminary efficacy, and pharmacodynamics of IV adrabetadex. The primary outcome will be the efficacy of adrabetadex to reduce plasma levels of an NPC bile acid biomarker, a cholesterol-derived NPC1 disease-specific biomarker that serves as a pharmacodynamic (PD) measure of the effect of the drug to reduce the oxidizable cholesterol pool in liver tissue. The secondary outcome measure will be the examination of the dose-response relationship for attenuation of liver dysfunction, as determined by reduction in serum transaminases (ALT and AST) and liver size. This study will also evaluate the effect of intravenous adrabetadex on a series of disease-associated serum biomarkers.

5.2 Subjects

Approximately 12 subjects will be diagnosed as having either NPC1 or NPC2 based on criteria specified in Section 5.4.1. Information about this study will be disseminated through patient support organizations and posted on ClinicalTrials.gov. The research group may facilitate diagnostic testing. Both genders will be enrolled. No exclusion will be based upon race or ethnicity.

5.3 Study Size, Duration and Location

The study will enroll approximately 12 subjects up to a maximum of 15 subjects to account for potential study withdrawals, discontinuations or unconfirmed diagnosis of NPC. It is anticipated that this study will take four years to complete, with approximately four subjects to be enrolled per year.

Study-related assessments will be conducted at St. Louis Children's Hospital.

For each subject, the first phase of the protocol will be conducted over seven weeks; one-week inpatient followed by five weeks outpatient administrations with a post-dose safety evaluation performed one week after the final dose. The second phase of the protocol will be an open label extension conducted in an out-patient setting over six months with a post-dose safety evaluation performed one week after the final dose.

5.4 Eligibility Criteria

5.4.1 Inclusion Criteria

1. Age 0 to 6 months of age at time of enrollment, both genders, and any race/ethnicity.

2. Diagnosis of NPC (either NPC1 or NPC2) based upon meeting any of the two following conditions:
   A. Two variants classified as pathogenic or likely pathogenic in *NPC1*/*NPC2* on clinical laboratory testing , or
   B. One variant classified as pathogenic or likely pathogenic on clinical laboratory testing and a positive NPC biochemical marker (oxysterol or bile acid biomarker or PPCS/Lyso509) test, if acid sphingomyelinase deficiency and cholesterol ester storage disease have been excluded either by clinical molecular testing of the SMPD1 and LIPA genes or by clinical biochemical assay for acid sphingomyelinase and lysosomal acid lipase enzymes (or a combination of enzymatic and molecular testing).
   Variants will be interpreted using the American College of Medical Genetics guidelines for the interpretation of sequence variants and testing must be performed by a CLIA-certified laboratory.

3. Subjects with evidence of NPC-related liver disease as defined by direct bilirubin (DB) >2mg/dL or DB/total bilirubin ratio >0.2.

4. Ability to travel to a research site.

5. Willing to participate in all aspects of trial design including serial blood collections.

6. Parent / guardian must provide written informed consent to participate in the study. Because of the age range intended for inclusion, assent will not possible.

5.4.2 Exclusion Criteria

1. Age > 6 months at time of enrollment in the trial.

2. A medical condition (such as clinically significant bleeding diathesis or evidence of immune suppression) that in the opinion of the investigator precludes placement of an intravenous catheter

3. An absolute neutrophil count (ANC) of less than 1,500 per microliter.

4. A platelet count less than 75,000 per microliter.

5. History of severe neonatal encephalopathy, per modified Sarnat including level of consciousness as stupor/coma, absent spontaneous activity, decerebrate posture, flaccid tone, absent suck, absent moro, diverted/nonreactive pupils, lack of heart rate variability, and apnea..

6. Subjects, who in the opinion of the investigators, are unable to comply with the protocol or have specific health concerns that would potentially increase the risk of participation. Examples of inability to comply include unwillingness to relocate or travel to a study site, suspected noncompliance with study procedures, behavior that jeopardizes the safety or security of the data or study staff, and other causes of inability to comply.

7. Concurrent participation in another investigational drug trial.

8. History of renal disease or evidence of acute kidney injury defined as serum creatinine greater than 1.5 mg/dL or an increase of at least 0.2-0.3 mg/dL per day.

5.5 Prior and Concomitant Medications

All concomitant medications will be recorded in the appropriate case report form (CRF).

5.6 Dosing and Dose Adjustments

Adrabetadex will be administered intravenously to specifically target liver disease. In the first phase of the study, dosing frequency will be twice a week with IV adrabetadex for six weeks for a total of 12 administrations. Subjects will be evaluated at each study visit for evidence of adverse effects.

Adrabetadex is provided as a 200 mg/mL solution and infused at this concentration and will be administered at a rate of 250 mg/kg/hr. A 5 kg infant receiving a 500 mg/kg dose, for example, will receive 12.5 ml of the 200 mg/ml solution.

Doses to be studied are 500 and 1000 mg/kg.

Six subjects will be studied at each dose level

Cohort 1	Subjects1-6	500 mg/kg
Cohort 2	Subjects 7-12	1000 mg/kg

The DSMC will review data from the first phase of the study for all six subjects in Cohort 1 prior to initiation of Cohort 2.

Subjects who do not tolerate (section 7.9) the initial 500 mg/kg dose may have the dose decreased to 250 mg/kg/ dose and remain at this dose for the remainder of the study.

Subjects who do not tolerate the 250 mg/kg dose will be withdrawn from the study.

Subjects who do not tolerate the first two doses of 1000 mg/kg dose may have the dose decreased to 500 mg/kg and remain at this dose level for the remainder of the study.

Subjects may be withdrawn for any Grade 3 AE (per NCI's CTCAE) possibly, probably or definitely related to study drug; any Grade 4 toxicity; any subject with pulmonary complications or evidence of renal injury; or determination that the limit of safety and/or tolerability has been reached. In the context of adrabetadex administration, limit of tolerability is defined as a sustained increased respiratory rate over 30 minutes or decreased Sa02 (<90%) resulting in need for, or increase in sustained need for supplemental oxygen, or evidence of renal injury as defined as a serum creatinine (SCr) rise > 0.5 mg/dl.

Subjects who demonstrate significant reduction either in the glycine-conjugated trihydroxycholanic acid biomarker or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) will be allowed to crossover into the second phase of the study, an open-label phase of six months duration. In this phase of the study, dosing frequency will be monthly with IV adrabetadex for six months for a total of six administrations. Subjects will be evaluated at each study visit for evidence of adverse effects.

5.7. Biological Specimens

Blood (serum and plasma) and urine will be collected as part of this protocol. Research samples will be stored locally or in the NICHD biorepository. Coded samples may be sent to collaborating laboratories, the NIH, and Mandos, LLC. Biomaterial collected as part of this study may be used for future research related to Niemann-Pick disease or other projects specifically approved by an Institutional Review Board. Priority will go to studies related to Niemann-Pick disease.

5.8 Non-study Drugs

This protocol will not provide non-study drugs.

5.9 Study Drug

Mandos, LLC will provide the study drug and support regulatory aspects of this study. Adrabetadex will not be provided under this protocol after completion of this study.

5.12 Withdrawal of Subjects from the Study

Subjects that are withdrawn from the study either by their choice or investigator action will be provided with written notification that their child was withdrawn from the study and provided with written recommendations regarding clinical follow-up.

6. Assessments, Procedures, and Testing

6.1 Medical History and Physical/Neurological Examinations

A medical and medication history will be obtained and a physical exam will be conducted after admission to the study center. This will ensure that the subject's medical health is adequate to participate in this study.

Subjects will be evaluated with an interim history and physical examination at least daily while admitted to the study center.

Anthropomorphic measures including weight and height will be obtained weekly in phase 1 and monthly in phase 2.

Physical and neurological examinations will be standardized.

6.2 Pulmonary Function Assessment

A baseline CXR and oxygen saturation will be obtained to assess placement of a peripherally inserted central catheter (PICC) and prior to the first administration of the study drug. CXR will only be repeated if clinically indicated.

6.3. Liver function assessment

In phase 1, plasma AST and ALT will be obtained at baseline, 2, 4 and 6 weeks. In phase 2, plasma AST and ALT will be obtained at baseline, 2, 4 and 6 months.

6.4 Abdominal Ultrasound

In phase 1, an abdominal ultrasound exam will be conducted at baseline and 6 weeks to determine liver size and spleen volumes. Liver size is determined by the liver's midclavicular longitudinal diameter (34). Organ volumes are the product of three long axes (longitudinal, transverse and anterior-posterior) (35).At the time of this abdominal ultrasound in phase 1, liver elastography will also be obtained. In Phase 2, an abdominal ultrasound with liver elastography will be repeated at the end of the six-month protocol.

6.5 Audiological Evaluation.

An audiological evaluation will be obtained at baseline and at conclusion of phase 1 of the study. Audiology assessment will be performed using otoacoustic emissions (OAE). This test does not require sedation.

6.6 Clinical Laboratory Tests

Clinical laboratory testing will be conducted by St. Louis Children's Hospital Clinical Laboratories.

6.6.1 Hematology/Chemistry

Blood samples for the clinical laboratory tests will be collected by a qualified person using either the central line, by indwelling catheter, or by venipuncture.

Testing will include the following (phase 1: 2.5 mls/time point; 10 mls total over six weeks, phase 2: 2.5 mls/time point; 10 mls total over six months):

Hematology: complete blood count (CBC) with differential and platelet count, and prothrombin time (PT).
Clinical chemistry: electrolytes, glucose, blood urea nitrogen (BUN), creatinine, AST, ALT, GGT, alkaline phosphatase, bilirubin (direct and total), albumin, calcium, magnesium, phosphorus, and CK.

In phase 1, testing will occur at baseline, 2, 4 and 6 weeks. In phase 2, testing will occur at baseline, 2, 4, and 6 months. For study subjects, the amount drawn will not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
Lab results do not need to be resulted and reported prior to dosing.

6.6.2 Urinalysis

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity and microscopic analysis. In phase 1, this testing will occur at baseline, 2, 4 and 6 weeks, and in phase 2 at baseline, 2, 4 and 6 months.
Lab results do not need to be resulted and reported prior to dosing.

6.7 Research Laboratory Testing

Plasma and serum will be collected for biomarker analysis. Sample collection, processing and storage will be standardized. Coded samples will be sent to NICHD Biorepository for long-term storage. Testing may be performed in clinical or research laboratories. Research testing will include, but is not limited to the following:

Markers of cholesterol homeostasis (phase 1: Baseline, 2, 4 and 6 weeks; 0.5 ml/time point; 2 mls total over 6 weeks; phase 2: Baseline, 2, 4 and 6 months; 0.5 ml/time point; 2 mls total over 6 months)

1. Trihydroxycholanic acid glycine conjugate (bile acid biomarker)
2. Cholestane-3β,5α,6β-triol
3. PPCS/Lipid-509

Plasma lipidomics (phase 1: Baseline and 6 weeks; 0.5 ml/time point; 1 ml total over 6 weeks; phase 2: 6 months; 0.5 ml/time point; 0.5 ml total over 6 months)

1. Sphingolipids: sphingoid bases, ceramides, glucosylceramides, lactosylceramides, gangliosides
2. Lysosphingolipids: lyso-sphingomyelin

Additional biomarkers for NPC (phase 1: Baseline, 2, 4, and 6 weeks; 1.75ml/time point; 7mls over 6 weeks; phase 2: Baseline, 2, 4, and 6 months; 1.75 ml/time point; 7 mls total over 6 months)

- Serum 24(S)-hydroxycholesterol
- Serum 27-hydroxycholesterol
- Serum neurofilament light chain

Lab results do not need to be resulted and reported prior to dosing.

6.8 Future Research and Other Testing

Other blood, cellular or urine biomarkers may be assessed. At the discretion of the investigator, blood, and urine may be collected and saved for future research.
Biomarkers of inflammation (phase 1: Baseline, 4 and 6 weeks; 0.5 ml/time point; 1.5 mls total over 6 weeks; phase 2: 6 months; 0.5 ml/time point; 0.5 mls total over 6 months)

Such as galectin 3 (LGAL3), cathepsin D, lysozyme, C-Reactive Protein High Sensitivity (hsCRP), and inflammatory cytokines

Bile acids (phase 1: Baseline, 2, 4 and 6 weeks; dried blood spot; total volume minimal; phase 2: Baseline, 2, 4 and 6 months; dried blood spot; total volume minimal)

The blood, urine, and derivatives thereof (e.g., peripheral B-cells, ribonucleic acid (RNA) or deoxyribonucleic acid (DNA)), collected under this protocol, can be stored for future research not specifically lined in this protocol. Such research could involve, but is not limited to, proteomic, genomic, biochemical, metabolomic, and molecular analysis of these samples. Corresponding clinical data may also be used for future research. Future research using these samples will relate to Niemann-Pick disease or other projects specifically approved by an Institutional Review Board. Priority will go to studies related to Niemann-Pick disease. This research may occur at the NIH or at outside laboratories. If sent to outside laboratories samples will be coded and patient identifiers will be removed. If a biospecimen is sent to a clinical laboratory for testing, identifiers will not be removed and the result will become part of the medical record.

6.9 Collaborating laboratories and entities

Dr. Patricia Dickson	Washington University, St. Louis, MO
Dr. Xuntian Jiang	Washington University, St. Louis, MO
Dr. Forbes D. Porter	NICHD, NIH, Bethesda, MD
Mandos, LLC	Thousand Oaks, CA

Additional laboratories can be added by amendment of this protocol.

7. Human Subjects Protections

7.1 Institutional Review Board

This protocol and informed consents will be reviewed and approved by the Washington University Institutional Review Board (IRB). The IRB will meet all FDA requirements governing IRBs (Code of Federal Regulations (CFR), Title 21, Part 56).

7.2 Ethical Conduct of the Study

The investigator will conduct this study in compliance with FDA regulations.

7.3 Patient Information and Informed Consent

Written informed consent will be obtained from parents or guardians prior to any intervention under this protocol. The informed consent form (ICF), as specified by the Washington University IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

Verbal or written screening for inclusion/exclusion criteria may be conducted prior to obtaining informed consent.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the guardians. The Principal Investigator or an Associate Investigator will obtain consent. The original signed and dated informed consent will be placed into subject's medical record. A copy will be given to the guardian.

7.4 Subject Selection

Subjects will be diagnosed as having NPC based on criteria specified in Section 5.4.1. For potential subjects for whom a definitive diagnosis is not available, the researchers may provide NPC-specific diagnostic testing before subject enrollment.

Information regarding this study will be distributed through parent support organizations such as, but not limited, to National Niemann-Pick Disease Foundation (NNPDF), Ara Parseghian Medical Research Foundation (APMRF), Dana's Angels Research Trust (DART), Support of Accelerated Research for Niemann-Pick Type C (SOAR-NPC), and Fight NPC.

Information about the study will be posted on ClinicalTrials.gov.

7.5 Gender and Ethnic/Racial Background

Subjects of either gender or any ethnic/racial background will be eligible for this study. NPC1 is an autosomal recessive disorder, thus gender distribution is expected to be equal. NPC1 is a panethnic disorder, but several genetic isolates, due to founder effects, exist. These include Acadians in Nova Scotia, Hispanics in parts of Colorado and New Mexico, and a Bedouin Group in Israel. It is expected that the subject's ethnic/racial demographics will reflect disease demographics. The small size of this study could result in random skewing of the expected distribution for either gender or ethnic/racial background.

This is a pilot study involving a small sample size from a limited patient population with a rare disease. Subjects will be screened to determine if they are eligible to participate in the trial prior to enrollment. Selection bias will be minimized as much as possible by screening all interested NPC subjects until the maximum accrual number has been met.

7.6 Research Involving Children

This study will involve physically and cognitively impaired children. Consent will be obtained from parents/guardians. If possible, consent will be obtained from both parents/guardians. Verbal consent can be given by a second parent/guardian if only one parent has accompanied the child to the study site. Due to the age range included in this study assent will not be possible.

This study is consistent with 45 CFR 46.405. Specifically, the research involves greater than minimal risk but presents the prospect of direct benefit to the individual child involved in the research. Given that NPC is a progressive, lethal neurological disorder with no FDA approved therapy, the risks in this protocol are commensurate with the disease process. The preclinical data in animal models suggest that the risk is justified by the potential benefit should this drug prove to be efficacious in humans.

7.7 Subject Withdrawal

Guardians/parents will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. Subjects may be withdrawn from the study for any of the following reasons:

- Parent/guardian request
- Parent/guardian is unwilling or unable to comply with the protocol
- Medical reason, at the discretion of the Investigator or Medical Monitor
- Occurrence of the following:
  a. any Grade 3 AE (per NCI's CTCAE) possibly or definitely related to study drug
  b. any Grade 4 toxicity
  c. any subject with pulmonary complications or evidence of renal injury
  d. determination that the limit of safety and/or tolerability has been reached. In the context of adrabetadex administration, limit of tolerability is defined as a new oxygen requirement or evidence of renal injury.
  e. evidence of development or worsening of liver synthetic function (monitored by serum albumin and PT) or evidence of development or worsening of hepatic encephalopathy (monitored by serum ammonia levels).

Although study treatment will cease, subjects will be encouraged to remain on study in order to collect all of the data prescribed in the protocol. The reasons for subject withdrawal will be recorded in the subject's CRF.

For a withdrawal due to a safety issue, subjects will be followed until the safety issue is resolved or returns to baseline level. Additionally, any appropriate referrals will be made as needed.

Any usable data from withdrawn subjects will be included in safety and efficacy evaluations. Withdrawn subjects may be replaced.

7.8 Adverse event assessments

Adverse events will be assessed using CTCAE version 5.0. Safety and tolerability of adrabetadex will be determined as presented in Table 1 except for respiratory and audiological complications.

Subjects will be withdrawn or dose decreased if they experience systemic (decreased blood pressure, heart rate, allergic rash, wheezing), respiratory (sustained increased respiratory rate over 30 minutes or decreased Sa02 (<90%)), or central nervous system (altered level of consciousness, seizures) symptoms during drug infusion or within 2 hours post-infusion. Subjects will be withdrawn or dose decreased if CXR demonstrates pulmonary infiltrates likely related to drug administration. If the etiology of pulmonary infiltrates is not known, they dose may be repeated and a subsequent CXR obtained. If the subsequent CXR demonstrates increased pulmonary infiltrates, subject will be withdrawn.

Table 1. Decision Table for Evaluating the Safety and Tolerability of IV adrabetadex in Individual Subjects (respiratory and audiological excluded)

	Safety Profile of Individual Patient	Safety Decisions*
A	No AEs and no SAEs or Any number of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 drug-related AEs; ≤ 1 CTCAE Grade 2 drug-related AE; or	Repeat the current dose
B	2 CTCAE Grade 2 drug-related AEs (or	Repeat the current dose, Study a lower dose (if applicable)
C	≥ 3 CTCAE Grade 2 drug-related AEs or ≥ 1 drug-related SAE	Study a lower dose, or withdraw the subject and Evaluate the risk/benefit profile for dose escalation of other subjects
D	Any CTCAE Grade 3 drug related AE; Any CTCAE Grade 4 drug-related AE; Any subject with drug-related pulmonary complications or thromboembolic complications Determination that the limit of safety and/or tolerability has been reached	Withdraw the subject and Evaluate the risk/benefit profile in other subjects for dose escalations to or above the dose resulting in Grade 3 toxicity and Temporarily or permanently halt study, pending DSMC review, if two subjects develop the same Grade 3 toxicity or if any subjectt develops a Grade 4 toxicity

7.9 Discontinuation or Temporary Suspension of the Study

The DSMC or Principal Investigator may terminate this study at any time for safety or administrative reasons. The DSMC or Principal Investigator will terminate the study if the occurrence of AEs or other findings suggests an unacceptable risk to the health of the subjects. The study will be interrupted if two subjects, based on two concurrent assessments, develop the same Grade 3 drug-related adverse event (unless related to disease progression of NPC), or if any subject that develops a Grade 4 adverse event, (unless the AEs are of an accidental nature that could not be reasonably attributable to adrabetadex or related to disease progression of NPC). Following review by the DSMC, the study may be resumed as planned, resumed with subjects at a lower dose or discontinued.

7.10 Potential Benefits and Financial Compensation

The treatment has the potential to provide benefit to the subject by reducing the effect of the underlying disease. In addition, this study will improve understanding of the safety and potential efficacy effects of administering IV adrabetadex in subjects with NPC1.

No financial compensation will be offered to subjects, guardians, or families. Travel, lodging, and per diem expenses may be covered per site policy.

7.11 Conflicts of Interest

NIH (Dr. Forbes D. Porter) has been awarded US Patent 8,497,122, entitled "Biomarkers for Niemann-Pick C Disease and Related Disorders," for use of oxysterols as biomarkers for Niemann-Pick C disease. NIH (Dr.

Forbes D. Porter) has filed patent applications for use of protein biomarkers in NPC1. Dr. Jiang has filed a patent application for the use of bile acid biomarkers in NPC1. Additional patent applications may be filed by institutions involved in this study that relate to the treatment or monitoring of therapy for NPC1.

Dr. Forbes D. Porter and NICHD have a Cooperative Research Agreement with Mandos, LLC for the development of intrathecal adrabetadex. Dr. Porter is an associate investigator on a Rush University protocol that supports expanded access for adrabetadex.

Mandos, LLC will provide adrabetadex. Mandos, LLC. may provide additional support to facilitate completion of this study. Mandos, LLC may use data obtained from this study to develop adrabetadex as a commercial product.

Collaborating or associate investigators may have funding or consulting relationships with pharmaceutical companies developing therapies for NPC1. Although these collaborating or associate investigators provide invaluable input, they are not directly responsible for the recruitment or enrollment of subjects into the Phase 1/2a protocol at the Washington University

8 Potential Risks and Discomforts

Individual procedures and associated personal risks are briefly described, below.

8.1 Medical Evaluations

There are no significant risks associated with the physical, neurological, and neuropsychiatric examinations. Multiple independent evaluations may be stressful to an infant. Clinical photographs or video may be obtained and these could potentially be embarrassing to some subjects.

8.2. Risk of Intravenous Adrabetadex

The risks of intravenous adrabetadex are not known. Animal studies and human experience with HPBCD and adrabetadex to date suggest that intravenous administration of adrabetadex is generally safe and well-tolerated; however, a major purpose of this study is to further evaluate the safety and tolerability of intravenous adrabetadex in NPC1 subjects, as well as dose-response as assessed by reduction in plasma biomarkers and reduction in serum transaminases and liver size.

IV administration of an experimental drug could have untoward consequences including permanent disability or death.

Known toxic effects from the cat disease model include acute respiratory distress and death, and apparent irreversible deafness:

- Cats receiving 8,000 mg/kg HPBCD by subcutaneous injection developed acute respiratory distress and died due to this complication.
- Cats receiving multiple subcutaneous doses of 4,000 mg/kg or a single subcutaneous dose of 8,000 mg/kg HPBCD developed apparent irreversible deafness (36).
- A majority of mice receiving a single 8000 mg/kg subcutaneous dose of HPBCD had hearing loss due to loss of outer hair cells (37). However, chronic dosing at 4000 mg/kg showed an initial hearing loss that subsequently recovered suggesting that homeostatic mechanisms could adjust to the lower dosing.
- Pulmonary toxicity has been reported in young pigs receiving IV HPBCD infusions (38). Infusion of 1 g/kg of 40% HPBCD in normal saline over 40 minutes resulted in cardiovascular instability. Five infusions over two weeks of 0.25-0.5 g/kg over 40 minutes resulted in inflammatory pulmonary changes.

No adverse events related to pulmonary function have been reported for the children receiving IV or IT HPBCD under individual use INDs cited in the initial IND. The investigators are not aware of any pulmonary adverse events being reported in the eight other individuals receiving IV HPBCD under expanded access INDs in the United States. Those individuals are typically receiving 2500 mg/kg HP-β-CD every week. Individuals in the US are receiving Kleptose HPB, from which adrabetadex is derived. Matsuo et al (33) reported in one subject transient diffuse pulmonary infiltrates and fever following infusions of IV HPBCD, which occurred after 23 months of therapy and in the context of recovery from an aspiration pneumonia. These resolved with prednisolone and antihistamine pretreatment and interpreted by the authors as a drug-related immunological reaction. The adverse pulmonary event appears to be related to high peripheral dosing. The HPBCD used by Matsuo et al is not the same preparation as adrabetadex.

While an allergic or anaphylactic reaction to adrabetadex is unlikely, the drug administration will take place in the Neonatal Intensive Care Unit, the Pediatric Intensive Care Unit, or the Infusion Center at St. Louis Children's Hospital, which provide close monitoring for acute adverse effects such as anaphylactic response to adrabetadex. Nursing and medical staff are trained in Code Blue procedures as well as Advanced Life Support, and many staff members are trained in Pediatric Advanced Life Support. Emergency resuscitation carts (Code Carts) are in place on every Patient Care Unit.

Exact doses for emergency resuscitation drugs for pediatric subjects (defined as less than 18 years of age) who weigh less than 50 kg are calculated immediately upon each admission and recorded on the Pediatric Emergency

Drug Sheet (PEDS). These include medications necessary for managing anaphylactic reactions (epinephrine, diphenhydramine and hydrocortisone). A copy of this document is kept on the subject's medical record as well as on the Code Cart on the Patient Care Unit for the duration of the admission. Code teams include a pediatrician.

8.3 Phlebotomy

Phlebotomy is a risk/discomfort of this study. An anesthetic cream such as EMLA is an option to reduce discomfort. Infection and bruising are possible at the site of the blood draw. T At each time point the maximum blood draw is 6 mL. In Phase 1, the maximum blood draw over 6 weeks is 24mL. In Phase 2, the maximum blood draw over 6 months will be 24mL. Nursing staff will monitor blood-drawing volumes. If blood limits are an issue, testing will be prioritized by the investigators. Safety laboratory tests will take priority over investigational testing. Not obtaining a test due to blood limit prioritization will not be considered a protocol deviation.

8.4 Audiological Evaluation

Otoacoustic emissions (OAE) monitors for ototoxicity. OAE test is used to find out how well the inner ear, or cochlea, works. OAEs are sounds given off by the inner ear when responding to a sound. While the infant or child is sleeping, a small earphone, or probe is placed in the ear. The probe puts sounds in the ear and measures the sounds that come back.

8.5 Sedation

Sedation for study procedures may be performed at the discretion of the research team in consultation with the guardians and anesthesiology. The medical and anesthesia clearance may determine that the subject is not fit for sedation during study procedures due to pre-existing medical conditions that would cause this elective procedure to be more risky. If that is the case, and sedation is necessary, the subject would be excluded from the study. If during the procedure complications of sedation arise or the level of sedation is inadequate, the procedure will be terminated.

The major risk associated with sedation is respiratory collapse. In order to minimize this possible complication, sedation will be performed by experienced pediatric physicians. Facilities for maintenance of a subject's airway, artificial ventilation, and circulatory resuscitation will be immediately available and ready for use. The anesthesiologist will also select the anesthetic agent used based on their clinical judgment. Another risk of sedation is aspiration. Intubation decreases the risk of aspiration and may be used if in the opinion of the anesthesiologist that it is indicated. Death is a rare complication of sedation when performed by a licensed anesthesiologist under controlled conditions.

8.6 Chest X-ray

A chest X-ray (CXR) will be obtained on the first admission to check placement of a peripherally inserted central catheter or other central IV line for drug administration, and this will serve as a baseline study should pulmonary symptoms be observed during the study.

There is no discomfort and minimal exposure to radiation with a CXR. X-rays usually have no side effects in the diagnostic range. The CXR is one of the lowest radiation exposure medical examinations performed today. The effective radiation dose from this procedure is about 0.8 mSv, which is about the same as the average person receives from background radiation in 10 days. Female participants should always inform any study coordinators, nurses and the x-ray technologist if there is any possibility that they are pregnant. The amount of radiation the subject will receive in this study is up to 0.04 rem, which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the US receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, cosmic radiation, and the earth's air and soil. If the subject/guardian would like more information about radiation, he/she will ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. The subject/guardian will inform one of the doctors if he/she has had any radiation exposure in the past year, either from other research studies or from medical tests or care, so the doctors can make sure that the subject will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into the subject's body. If the subject is pregnant or breast feeding, she may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults.

8.7 Liver/Spleen Ultrasound

The risks of an abdominal ultrasound are limited to mild discomfort of the technicians pressing the probe against the abdominal wall.

8.8 Peripherally Inserted Venous Catheter (PICC) and Risks

Insertion of a peripherally inserted venous catheter (PICC line) or other central IV line may be required for administration of the adrabetadex drug in this study due to the limited peripheral IV access in the neonatal patients, the dosing frequency, and the number of doses. The preferred central IV line of choice is a PICC line. In situations where a PICC of insufficient gauge to support the IV infusion and compliance with protocol activities, or where an indwelling central line is otherwise medically indicated, alternative central IV lines, such as a Broviac, can be used for drug delivery. In the open label extension, the increased age of the patients and reduced dosing frequency will permit administration of the drug via peripheral IV access. Study procedures will be performed at a high-volume center with a dedicated pediatric service. At the time of subject consent, there will be discussion with the parents or guardian regarding the nontherapeutic nature of the PICC line procedure and the requirement for procedural sedation. A centrally placed, venous catheter is required for administration of adrabetadex. For this study, we expect to utilize a PICC line. The PICC line will be placed by a qualified and experienced person. In the neonatal population, insertion of a PICC line is normally accompanied by sedation and will not be withheld to avoid its risks. Rare risks associated with this procedure include bleeding at the site of insertion, thrombosis on or in the catheter, and systemic infection.

9. Study Procedures and Schedule

9.1 Overview of Study

Subjects who have been screened for eligibility will be admitted to the Neonatal Intensive Care Unit or the Pediatric Intensive Care Unit depending on age for inpatient baseline qualification assessments after written informed consent has been obtained. In phase 1 of the study, the first admission will last approximately 7 days. Subjects may then be followed as outpatients for the subsequent five weeks, or they may remain inpatient if clinically indicated. Upon initiation of the study, a PICC line or other intravenous access will be placed and baseline laboratory testing and liver/spleen ultrasound will be obtained. Drug will be administered twice a week with an interval of 4 ± 1 days. A total of 12 doses will be given. Subjects who demonstrate significant reduction either in the glycine-conjugated trihydroxycholanic acid biomarker or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) will be allowed to crossover into the second phase of the study, an open-label phase of six months duration. In this phase of the study, dosing frequency will be monthly with IV adrabetadex for six months for a total of six administrations. Subjects will be evaluated at each study visit for evidence of adverse effects.

9.2 Subject Screening

Review of eligibility may be performed through chart review, written query or via telephone. Medical records may be requested. A screening log will be maintained indicating status.

9.2 Outline of Protocol Admissions and Testing

Time	Major Events	Admission Type	Length
Phase 1			
Week 1	Enrollment and consent PICC/IV line placement Liver/spleen ultrasound Obtain baseline laboratory testing Administration of 1st and 2nd dose	Inpatient	7 days
Weeks 2-6	Administration of doses 3-12 Obtain laboratory testing	Outpatient*	10 days
Week 6	Liver/Spleen ultrasound PICC line removal	Outpatient*	1 day
Week 7	Post-dose safety evaluation	Outpatient*	1 day
Phase 2			
Month 1	Initiation of open-label extension one month ±7 days month after dose 12 Obtain baseline laboratory testing Administration of dose 13	Outpatient*	1 day
Months 2-6	Administration of doses 14-18 Obtain laboratory testing	Outpatient*	1 day
Month 6	Liver/Spleen ultrasound Post-dose safety evaluation	Outpatient*	1 day

*May be performed as inpatient if the patient remains hospitalized

9.3 Baseline Admissions

Subjects who have been screened for eligibility will be admitted to the Neonatal Intensive Care Unit or the Pediatric Intensive Care Unit for baseline qualification assessments. Written informed consent will be obtained. Baseline evaluation will include the following:

1. Admission to the clinical research unit
2. Confirmation of eligibility
3. Collect vital signs including temperature, respiration, SaO_2, heart rate, and blood pressure
4. History and physical examination and neurological assessment
5. Collect blood and urine samples for clinical and research laboratory testing
7. Audiological evaluation
8. Abdominal ultrasound (liver and spleen volume)
9. Placement of a PICC line or other IV access
10. CXR

9.4 First Two Intravenous Drug Administrations

Subjects will be admitted to the Neonatal Intensive Care Unit or the Pediatric Intensive Care Unit for 7 ± 2 days. IV adrabetadex is provided as a 200 mg/mL solution and will be administered undiluted via PICC or other central line at a rate of 250 mg/kg/hr. A 5 kg infant receiving a 500 mg/kg dose, for example, will receive 12.5 ml of the 200 mg/ml solution. The 20% solution is isotonic with an osmolarity of 290 ± 30.0 mOsm/kg and is suitable for delivery through central IV access.

Rate may be decreased in 25 mg/kg/hr increments to 175 mg/kg/hr if required. The rate and reason for reduction will be recorded. Dose will be either 500 or 1000 mg/kg.

For study participants in whom a PICC line or other central line cannot be placed, adrabetadex may be administered via peripheral IV. If administered via peripheral IV, adrabetadex will be diluted 4-fold into sterile saline prior to infusion. A 5 kg infant receiving a 500 mg/kg dose, for example, will receive 50 ml of the diluted adrabetadex (50 mg/ml solution).

Vital signs (temperature, heart rate, respiratory rate, supine blood pressure, and SaO_2) and standard neurological checks will be conducted at least every 30 minutes during and then for the first two hours after drug administration, then every 2 hours until 6 hours post infusion, and then at least every 6 hours until 24 hours post infusion for the first two drug infusions.

Abnormal vital signs that meet criteria to be classified as adverse events according to section 11 will be reported as adverse events.

9.6 Doses 3-12

These drug administrations may occur as an outpatient. Interval between dosing will be 4 ± 1 days.

IV adrabetadex will be administered IV at a rate of 250 mg/kg/hr. Rate may be decreased in 25 mg/kg/hr increments to 175 mg/kg/hr if required. The rate and reason for reduction will be recorded.

Vital signs (temperature, heart rate, respiratory rate, supine blood pressure, and SaO_2) and standard neurological checks will be conducted at least every 30 minutes during and then for the two hours after drug administration. Subject may be discharged 2 hours post administration if no issues.

9.7 Phase 1: Final Evaluation

The final evaluation will occur 2 ± 1 days after the 12^{th} adrabetadex infusion. This will include a liver/spleen ultrasound. PICC line will be removed.

9.8 Post-dose Safety Evaluation

Subject will be evaluated by history 7 ± 2 days after the 12th adrabetadex infusion. History will be taken in person or by telephone by the study coordinator and consist of an interim medical history. The study coordinator will document the conversation and history. If discharged to home then study team will follow-up by phone on a weekly basis for two additional weeks.

9.9 Phase 2: Open-Label extension (Doses 13-18)

Subjects who demonstrate significant reduction either in the glycine-conjugated trihydroxycholanic acid biomarker or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) will be allowed to crossover into the second phase of the study, an open-label phase of six months duration. In this phase of the study, dosing frequency will be monthly with IV adrabetadex for six months for a total of six administrations. Subjects will be evaluated at each study visit for evidence of adverse effects.

Entry into the open-label extension phase will occur after completion of phase 1 final evaluation. Doses 13-18 may be administered as an outpatient. In the extension phase, the subjects will continue at the same dose (mg/kg) as they received for the 12th adrabetadex infusion.

Because the adrabetadex drug will be infused through peripheral IV access for doses 13-18, the 200 mg/mL solution will be diluted 4-fold into sterile saline prior to infusion. A 5 kg infant receiving a 500 mg/kg dose, for example, will receive 50 ml of the diluted adrabetadex (50 mg/ml solution).

IV adrabetadex will be administered via peripheral IV access at a rate of 250 mg/kg/hr. Rate may be decreased in 25 mg/kg/hr increments to 175 mg/kg/hr if required. The rate and reason for reduction will be recorded.

Vital signs (temperature, heart rate, respiratory rate, supine blood pressure, and SaO_2) and standard neurological checks will be conducted at least every 30 minutes during and then for the two hours after drug administration. Subject may be discharged 2 hours post administration if no issues.

If there is evidence of clinical deterioration during the open label phase (based on assessment by the patient's physician), dosing frequency may be increased. Increasing dosing frequency more frequently than monthly will necessitate reinsertion of a PICC line (see Section 8.8).

9.10 Phase 2: Post-dose Safety Evaluation

Subject will be evaluated by history 7 ± 2 days after the 18th adrabetadex infusion. History will be taken in person or by telephone by the study coordinator and consist of an interim medical history. The study coordinator will document the conversation and history. If discharged to home then study team will follow-up by phone on a weekly basis for two additional weeks.

9.11 Adrabetadex dose

The subjects will be enrolled in two cohorts.

Two dose levels will be evaluated. Dose levels for each cohort are:

Cohort 1	500 mg/kg
Cohort 2	1000 mg/kg

Subjects who do not tolerate the first dose of 500 mg/kg dose may have the dose decreased to 250 mg/kg dose. Subjects who do not tolerate 250 mg/kg dose will be withdrawn from the study. Subjects who do not tolerate the

first two doses of the 1000 mg/kg dose may have the dose decreased to 500 mg/kg. Decisions regarding tolerability will be made by the DSMC in conjunction with the investigators and local monitor.

If a subject withdraws from the protocol prior to the 12th drug infusion, they may be replaced.

10. Statistical Analysis Plan

This Phase 1/2a study is intended to provide safety, tolerability, pharmacodynamic, and pharmacokinetic data that will be critical to assessing the feasibility, design, and conduct of future studies in the NPC1 population. As part of this trial we will test whether biochemical response of plasma biomarkers, serum AST/ALT, or abdominal ultrasound can be used to guide identify a biochemically, and potentially a clinically, effective dose. These data would potentially guide the development of a future Phase 2/3 trial.

Assessment of safety and tolerability will be made by evaluation of summary statistics of adverse events and unanticipated problems. One purpose of this trial is to obtain pilot data on clinical outcome measures and biomarkers to identify outcome measures that appear to respond to therapy and to inform power calculations for a subsequent trial focused on establishing therapeutic efficacy.

The primary outcome measure for this trial is the plasma NPC1 bile acid biomarker. This bile acid is a metabolite of cholesterol, is elevated >99% of NPC1 subjects, is largely generated in the liver and therefore provides a biochemical measure of oxidizable lysosomal unesterified cholesterol in liver tissue (21). Serial plasma bile acid biomarker concentrations were measured in two NPC1 subjects over four years, during which period IV HP-β-CD treatment was initiated under an individual expanded use Investigation New Drug application. Following initiation of treatment, plasma bile acid biomarker concentrations were decreased by 46% and 62% in Subjects 1 and 2 after 3 and 9 months of treatment ($p<0.05$), respectively, and was even lowered into the normal reference range (<24.5 ng/ml) in Subject 2. Plasma bile acid biomarker concentrations were measured in a third NPC1 subject receiving weekly IV adrabetadex also under an individual expanded use Investigation New Drug application. Plasma bile acid biomarker concentrations were decreased by 75% after 6 weeks of therapy, with the trihydroxycholanic acid glycine conjugate concentration was lowered into the normal reference range (<13.5 ng/ml).

These data from three subjects previously treated with IV adrabetadex support the utility of this plasma NPC biomarker as a potential outcome measure to monitor the effects of IV adrabetadex on peripheral tissues. Utilizing this data, we would have approximately 80% power to detect a 33% reduction in the plasma biomarker concentration in 5 subjects. Utilizing this data, we would have approximately 57, 80 and 99% power to detect a 25, 33 and 50%, respectively, reduction in plasma biomarker concentration in 5 subjects.

The secondary outcome measure for this trial is the plasma AST and ALT levels.

For group comparisons, such as comparing mean values of primary outcome measurements, the statistical significance of differences in mean values will be determined by a two-tailed single-factor ANOVA or Student's t test. To perform correlations, such as for comparison of primary/secondary outcome data with NIH severity scale values or clinical assessments, data will be analyzed using Pearson and Spearman correlations, as appropriate. A p-value of 0.05 or less was considered significant. A Bonferroni posttest correction will be used to adjust for multiple comparisons (e.g., when analyzing the panel of secondary outcome measures).

11. Adverse Events, Protocol Deviations, and Data Safety Monitoring

11.1 Definitions

Adverse event: An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction: This is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-Threatening AE or Life-Threatening Suspected Adverse Reaction: An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the Investigator/Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event or Serious Suspected Adverse Reaction: An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the Investigator/Sponsor, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect

Unexpected AE or Unexpected Suspected Adverse Reaction: An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the protocol or consent or is not listed at the specificity or severity that has been observed.

11.2 Adverse Event Classification

Relationship to Investigational Drug: The following two classifications should be used when evaluating the relationship of AEs and serious adverse events (SAEs) to the investigational drug:

- **Unrelated:** No relationship between the experience and the administration of study drug; rather, related to other etiologies such as concomitant medications or subject’s clinical state. The reaction can be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject.

- **Related:** A reaction that follows at least a plausible temporal sequence from administration of the study drug.

11.3 Severity of an Adverse Event

Severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Published: 27 NOV 2017; v.5.0):

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

11.4 Monitoring of Adverse Event Data

The investigators will review each subject weekly during an admission. This may be by group email or conference call.

A local monitor and an independent Data Safety Monitoring Committee (DSMC) will review data on subjects completing and enrolled in the study. Review will occur after the first two subjects complete the study, and after each additional subject completes the study. Review may occur earlier if indicated by clinical circumstances.

11.4.1 Review of Safety and Tolerability

The evaluation of tolerability of a dose in an individual subject will be reviewed by the Principal Investigator with input from the Protocol Investigators, local monitor, and the DSMC. See **Table 1**.

11.4.2 Review of Respiratory Compromise

The study will be discontinued if two subjects demonstrate respiratory compromise associated with drug infusion at 500 mg/kg dose. If three subjects demonstrate drug related respiratory compromise associated with drug infusion in cohort two (1000mg/kg group) dosing for all remaining subjects (cohort 2) will be decreased to 500mg/kg.

11.4.3 Review of High Frequency Hearing Loss

Although not anticipated at the doses being evaluated, high frequency hearing loss is an expected complication of adrabetadex administration.

11.5 Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will review safety data from this study after the first two subjects complete the study and after each additional subject completes the study. Members will be “independent” in that they have no other involvement in the study. The DSMC will review data from each cohort prior to dose escalation. The DSMC will submit brief safety reports to the sponsor-investigator regarding the safety and progress of the trial. The DSMC may also meet ad hoc at the request of the sponsor-investigator. A local monitor, also independent to the study, will review reports to and from the DSMC. Reports from the DSMC and local monitor will be submitted to the institutional IRB along with a recommendation from the local monitor as to whether the study should continue with modification, continue without modification, or terminate.

11.6 Documentation of Adverse Events

Subjects will be evaluated and interviewed to identify AEs during the course of the study. AEs may also be identified through clinical and neurological examinations, laboratory tests, etc. Any events occurring prior to dosing will be recorded on the Medical History CRF. Events occurring after administration of the first dose of study medication will be recorded on the AE CRF. AE that occur up to and including 30 days after administration of the last dose of study drug must be reported.

All AEs spontaneously reported by the subject or in response to a question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event Form for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered

an AE and must be recorded on the AE CRF, unless otherwise stated in the protocol. AE information recorded on AE CRFs will be entered into the database on an ongoing basis.

For SAEs, a Serious Adverse Event Form must also be completed with as much information as possible and submitted in the time frame described below. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the subject was hospitalized, a copy of the discharge summary and any other relevant hospital records (e.g., admission report, laboratory test results, etc., must be included as part of the patient medical file).

All AEs considered to be related to study medication and all SAEs will be followed until resolved or until stable.

11.7 Notification about Serious Adverse Events and Serious Unexpected Adverse Reactions

11.7.1 Investigator Reporting

Investigators must report any SAE, whether or not considered drug related, including those listed in the protocol or Investigator Brochure. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

The study site will document all SAEs that occur (whether or not related to study drug) on the appropriate SAE form. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAEs must be submitted within 24 hrs and will be reviewed by the principal investigator or qualified designee and reported to the FDA and IRB according to applicable regulations and guidance. The site, within 48hrs, will submit all copies of the submitted MedWatch Form FDA 3500 to safety@mandoshealth.com.

SAE's will be reported to the responsible IRB per institutions policy.

SAE Reporting Contact Information:

Sponsor/Principal Investigator:
Patricia Dickson, MD
4444 Forest Park Ave
St. Louis, MO 63110
(314) 273-2943
pdickson@wustl.edu

Medical Monitor
Phillip Tarr, MD
One Children's Place
St. Louis, MO 63110
(314) 454-6173
tarr@wustl.edu

11.7. Adverse Events Exempt from IRB Reporting

The following will not be reported to the IRB as AEs:

1. Findings present at initial evaluation;
2. Abnormal laboratory tests that have no clinical consequence;
3. Abnormal clinical tests in which the clinical response would be considered standard care (such as iron supplementation of iron deficiency anemia), and are unlikely to be related to the protocol.
4. Problems listed in Table 2 unless an increase in frequency is noted.

Table 2. Adverse Events Associated with NPC1

Category	Adverse Event
HEENT	Eyes Ptosis Abnormal eye movements (including vertical supranuclear gaze palsy and abnormalities of both vertical and horizontal eye movements)
	Audiologic Progressive high frequency hearing loss Abnormalities in Auditory Brain Stem Responses
	Oromotor/Speech Dysarthria Dysphagia, choking/gagging on food or saliva Copious secretions/drooling
Respiratory	Aspiration
	Aspiration pneumonia
	Sleep apnea
Gastrointestinal/ Genitourinary	Hepatomegaly
	Elevated liver enzymes
	Splenomegaly
	Gastrostomy tube related to dysphasia
	Bladder/bowel incontinence
	Diarrhea
	Constipation
Lymphatic	Enlarged tonsils and adenoids
Hematologic	Epistaxis
	Thrombocytopenia
	Decreased serum iron, % saturation (not typically associated with low MCV)
Musculoskeletal/Extremities	Hyperreflexia, clonus
	Motor impairment Gross motor ataxia, impaired ambulation, balance, coordination, decreased muscular strength, muscle contractures Fine motor ataxia, tremor
Neurological	Seizures
	Cognitive Impairment:
	Learning difficulty, long/short term memory loss
	Sleep Disruptions:
	Gelastic cataplexy
	Narcolepsy
	Sleep schedule inversion
	Fatigue, daytime sleepiness
Psychiatric/Behavioral	Mood swings, diagnosis of major depressive disorder, bipolar disorder, schizophrenia
	ADD/ADHD diagnosis (not more common than in general pediatri population)

ADD: attention deficit disorder; ADHD: attention deficit hyperactivity disorder; HEENT: head, eyes, ears, nose, throat; MCV: mean corpuscular volume

11.8 Protocol Deviations

The following anticipated minor deviations in the conduct of the protocol will not be reported to the site IRBs unless they occur at a rate greater than that which is anticipated to occur (frequency will be assessed on a 12 month basis).

	Expected Frequency
Inability to obtain a blood or urine sample	15%
Technical issues preventing analysis of a blood Sample (e.g. hemolysis)	15%
Procedure or sample not obtained at specified time	15%
Drug administration occurring outside of defined time range	10%

Not obtaining a test due to blood limit prioritization will not be considered a protocol deviation.

12. Investigational Product

12.1 Identify of the Investigational Product

Adrabetadex will be provided to the pharmacies at the St. Louis Children's Hospital as a 200 mg/ml injectable solution in 100 ml vials.

The formulation of adrabetadex involves dissolving the Active Pharmaceutical Ingredient in water for injection, adding sodium chloride to 0.9% w/v and adjusting the pH if necessary with 0.01N sodium hydroxide and brought to the final volume with water for injection. The product is a clear, colorless solution that is free from visible foreign matter.

The investigational product will be labeled as an investigational product with the drug name, concentration and dosage instructions.

The St. Louis Children's Hospital pharmacy will dispense the product for administration by the Patient Care Unit.

12.2 Storage of the Investigational Product

Investigational product should be stored between 15-25 °C.

12.3 Investigational Product Accountability

The St. Louis Children's Hospital pharmacy is responsible for the accountability of the investigational product. This will include documentation of receipt, storage, and dispensing of the investigational agent. The St. Louis Children's Hospital pharmacy will return or destroy (per instruction of the IND sponsor) unused investigational drug at the conclusion of the study.

13. Study Administration

Quality assurance and quality control systems with written SOPs will be implemented and maintained to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

An external monitoring service will be used for monitoring. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The Clinical Monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.1 Data Handling and Recordkeeping

13.1.1 Electronic Data

Clinical data will be stored into REDCap, a secure, web-based application available through the Clinical and Translational Science Award (CTSA) at WUSM.

13.1.2 Case Report Form Completion

CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator will maintain copies of the CRFs at the study site. Completed electronic CRFs are to be signed off by the Investigator or his/her designee.
For subjects who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate CRF.

In addition, electronic data capture will be used for the study. Clinical data are entered into REDCap, a secure, web-based application available through the Clinical and Translational Science Award (CTSA) at WUSM. Access to our REDCap system is protected by multiple layers of security, running on Linux platforms configured for strict user permission policies. Our REDCap database is hosted on scalable cloud based services hosted in the WUSM secure network. User access is provided via an external secure web server. All web communication between the user web browser and the web server is SSL encrypted. Further protections are provided via strict Linux permission configurations on the servers themselves.

All database transactions are continually backed to facilitate PITR (point in time recovery) methods and are stored for approximately 30 days. Uploaded files are stored on secure cloud services and are only accessible via the WUSM secure network.

Access to the data and various systems are protected by WUSTL Key authentication per University best practices.

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13.1.3 Retention of Study Records

The Investigator will maintain all study records according to ICH/GCP guidelines and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. If a custodial change occurs, it must be documented.

13.2 Confidentiality

To maintain subject privacy, all CRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from NIH. It is understood that there is an obligation to provide complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants, as required.

13.3 Publication Policy

All information concerning use of adrabetadex in the context of this trial is considered confidential and shall remain the property of the investigators. In accordance with NIH policy, data will be shared outside of the consortium group principally through publications and presentations at scientific conferences. Publications reporting the results of this trial will be submitted in a timely way. Data will be made available to Mandos, LLC under a Cooperative Research Agreement. There are no anticipated delays or impediments to free publication of these results regardless of the outcome.

13.4 Direct Access to Source Data

The Investigators will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.), in addition to CRFs.

13.5 Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment and receive written approval by the IRB prior to implementation, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). Sponsor and regulatory authorizes will be notified as appropriate.

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