PROTOCOL TITLE: Topiramate for infants receiving whole body cooling in neonatal encephalopathy

**NCT01765218**

Document Submission Date to IRB 6/6/2018
Last IRB Review of Study 3/28/2023

## 1) Protocol Title

Title: Topiramate for infants receiving whole body cooling in neonatal encephalopathy

Protocol Version Date: May 25th, 2018

## 2) Objectives

a) Specific Aims: To determine the effect of adjuvant topiramate treatment on the outcome of newborns with perinatal depression (including neonatal encephalopathy) who are already receiving the therapeutic whole body cooling.

b) Hypotheses: We hypothesize that adjuvant therapy with topiramate will reduce short term disease severity in infants with neonatal encephalopathy/perinatal depression who are receiving whole body cooling. Specifically, we hypothesize that adjuvant topiramate will reduce the incidence of seizures (the primary outcome) in these infants. Secondary objectives include assessing the effect of that adjuvant topiramate in infants with neonatal encephalopathy/perinatal depression on biochemical markers of neuronal damage (serum UCHL1/ urine S100ß levels), a composite score of aEEG/cEEG abnormality, and on developmental outcomes at 9m, 18m and 27m.

c) Scientific Problem: Neonatal encephalopathy is a devastating and unexpected disease in newborns that affects 1.5 to 2.6 per 1000 live births (Kurinczuk 2010). Neonatal encephalopathy has a mortality rate of up to 30% and survivors are at significant risk for adverse outcomes, including seizures, cerebral palsy, and neurodevelopmental delay. Until recently, only supportive care could be offered to these infants, and no therapy was available to modify the natural history of the disease. However, therapeutic hypothermia, or whole body cooling, has been shown to be beneficial for these infants. Hypothermia reduces mortality and decreases the risk of moderate to severe handicap in survivors. (Shankaran 2005).

Although whole body cooling is effective at reducing the mortality and morbidity of neonatal encephalopathy/perinatal depression, the long-term outcome for such babies remains poor. For example in a recent NICHD funded study, whole body cooling reduced the rate of death but had no significant effect on long-term neurodevelopmental outcome of the survivors or moderate or severe disability from 62% to 44% (Shankaran 2012).

As the number of surviving newborns with neonatal encephalopathy undergo cooling increases there is an urgent need for additional pharmacological intervention to improve their outcome. A recent study reviewed Erythropoietin (Epo) as potential neuroprotective therapy in newborns undergoing whole body cooling if given in the first 1-2 weeks of life. This study was a Phase I/II Clinical Trial, “NEATO”, which revealed that when Epo was given with hypothermia it’s dose achieved/exceeded concentrations that are known to be neuroprotective in animals (Wu 2013). A more recent study, “HEAL”, high-dose erythropoietin for asphyxia and encephalopathy, found similar results that high dose Epo given with hypothermia for neonatal encephalopathy may result in less MRI brain injury and improved motor function by 1 year (Wu 2016).

These new results of present studies are rather interesting; yet there still remains potential for further exploration being that we have not started utilizing

these newer findings in our routine care/treatment of neonatal encephalopathy. It is imperative that continuing studies investigate any other potentials therapies that could be neuroprotective and improve neurodevelopmental outcomes in the long-term for these infants undergo whole body cooling.

**3) Background**

The demonstration that a *post-hoc* intervention (i.e. beginning after the initial CNS insult) such as whole body cooling, can have beneficial effects has generated increased interest in the use of other adjuvant neuroprotective therapies in newborns receiving therapeutic hypothermia. Several potential adjuvant therapies are currently under investigation to improve the outcome of these babies. Erythropoietin for example has demonstrated potential neuroprotective effects (Wu 2012/2016).

We propose to study the adjuvant use of topiramate. We have selected this agent for several reasons:

1. There are sound theoretical reasons why topiramate would be expected to improve outcome in neonatal encephalopathy. Neuronal damage following an ischemic event occurs in two waves, and glutamate plays a central role in both of these. Indeed, CSF glutamate levels in neonates following neonatal encephalopathy are strongly predictive of the degree of long-term impairment. Topiramate is effective at reducing glutamate release and this appears to be its prime biochemical action (Follet 2004).

2. There is encouraging animal data on the effectiveness of topiramate in rodent (Noh 2006, Sfaello 2005) and porcine (Schubert 2005) models of neonatal encephalopathy, and topiramate may increase the therapeutic time window for initiation of therapeutic hypothermia (Liu 2004).

3. There is good data on the safety of topiramate in neonates, including those with neonatal encephalopathy receiving whole body cooling. Topiramate is a widely used anticonvulsant in neonates (Novotny 2010). It has gained widespread acceptance because unlike phenobarbital and phenytoin (the traditional first-line agents), it does not lead to apoptosis in developing brain. A survey in 2008 (Silverstein) found that 55% of pediatric neurologists recommend topiramate for the treatment of neonatal seizures. Infants with neonatal encephalopathy and whole body cooling are a particularly high-risk group of neonates and both the underlying disease state (perinatal depression) and the treatment (whole body cooling) could alter the pharmacokinetics of topiramate. However, there is now good published peer-reviewed evidence of the pharmacokinetics of topiramate in neonates with neonatal encephalopathy who are being treatment with whole body cooling (Filippi 2009). Based on this data a safe and effective dose of topiramate was determined. Furthermore, there is also good peer-reviewed data on the safety of topitimate in neonates with neonatal encephalopathy who are being treated with whole body cooling (Filippi 2010), receiving doses used in the previous pharmacokinetic study.

Although we now have good evidence on the appropriate dose of topiramate in newborns with neonatal encephalopathy/perinatal depression receiving whole body

cooling, and data on its safety, there is currently no published data on its efficacy in human newborns. The proposed study aims to address that deficit.

References:

Filippi L, la Marca G, Fiorini P, Poggi C, Cavallaro G, Malvagia S, et al. Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia. 2009;50(11):2355-2361.

Filippi L, Poggi C, la Marca G, Furlanetto S, Fiorini P, Cavallaro G, et al. Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J Pediatr. 2010;157(3):361-366

Follett PL, Deng W, Dai W, Talos DM, Massillon LJ, Rosenberg PA, Volpe JJ, Jensen FE. Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. J Neurosci. 2004 May 5;24(18):4412-20.

Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86(6):329-338.

Liu Y, Barks JD, Xu G, et al. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. Stroke 2004;35(6):1460–5

Noh MR, Kim SK, Sun W, Park SK, Choi HC, Lim JH, Kim IH, Kim HJ, Kim H, Eun BL. (2006) Neuroprotective effect of topiramate on hypoxic ischemic brain injury in neonatal rats. Exp Neurol 201:470–478.

Novotny E, Renfroe B, Yardi N, Nordli D, Ness S, Wang S, Weber T, Kurland CL, Yuen E, Eerdekens M, Venkatraman L, Nye JS, Ford L (2010) Randomized

trial of adjunctive topiramate therapy in infants with refractory partial seizures. Neurology 74:714-720.

Schubert S, Brandl U, Brodhun M, Ulrich C, Spaltmann J, Fiedler N, Bauer R. Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. Brain Res. 2005 Oct 5;1058(1-2):129-36.

Sfaello I, Baud O, Arzimanoglou A, Gressens P. Topiramate prevents excitotoxic damage in the newborn rodent brain. Neurobiol Dis. 2005 Dec;20(3):837-48.

Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353(15):1574-1584.

Shankaran S, Pappas A, Mc Donald, SA, Vohr BR, Hintz, SR, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med 2012;366:2085-92

Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatric Neurol 2008; 39:77-9

Wu YW, Bauer L, Ballard R, Ferriero D, Glidden D, et al. Erythropoietin for Neuroprotection in Neonatal Encephalopathy: Safety and Pharmacokinetics. Official Journal of the AAP, Pediatrics 2012 Oct; 130 (4) 683-691.

Wu YW, Mathur AM, Chang T, McKinstry RC, Mulkey SB, et al. High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial. Pediatrics. 2016. June;137(6).

## 4) Inclusion and Exclusion Criteria

Newborn infants diagnosed with neonatal encephalopathy undergoing cooling therapy for neonatal encephalopathy irrespective of gender or race are eligible for this study. We aim to recruit patients both in English and Spanish.

All four of the following criteria must be met to qualify for the cooling protocol

1. Age: <u>less than</u> 1 day old
2. Gestational age > 35wks
3. Evidence of birth depression, <u>either</u>
   a. 10 minute Apgar score less than 5
   b. Need for cardiopulmonary resuscitation at 10 minutes of age
   c. Blood pH < 7.0 within the first 1-hour of life
   d. Base excess lower than -12 (i.e. base deficit more than 12) within the first hour of life
4. Evidence of encephalopathy based on clinical (neurological examination) or on aEEG/cEEG assessment**.**

**Exclusion Criteria:**

1. Major congenital or genetic abnormalities
2. Infants more than one day old
3. Known allergy/sensitivity or any hypersensitivity to components of study drug
4. Maternal illicit drug or alcohol use during pregnancy
5. If the baby had a proven (i.e. electrically confirmed seizure) prior to enrollment

**5) Study Timelines**

We expect to complete this study within 2 years. We have 13 patients already enrolled and our goal is 42 total (study arm n=21 and control arm n=21). We have chosen a sample size of 42 as this sample size will have an 80% chance of detecting a reduction of seizure rate by 2/3 with a p-value of 0.05.

At our institution alone we have ample experience in whole body cooling having cooled 31 patients in 2015, 28 patients in 2016, and most recently 26 patients in 2017. Patients will be asked to come for a one hour follow up outpatient clinic (MIND Institute) visit at the at 9, 18, and 27 months of age (all infants who receive cooling are asked to complete this follow-up, including those not in this study).

6) **Study Endpoints**

Our primary study endpoint remains to conclude if our current modality of whole-body cooling coupled with topiramate results in seizures or no seizures.

As well to determine the effect of adjuvant topiramate treatment on the outcome of newborns with perinatal depression (including neonatal encephalopathy) who are already receiving the therapeutic whole body cooling.

**7) Informed Consent**

One or both parents of the eligible infants are approached either

(1) In person in the NICU at UCDMC by one of the investigators

(2) By our Transport Nursing staff or Neonatal Fellow (if they are still at the outside referral center)

In either case, the details of the study its risks and potential benefits will be explained by an investigator, and the parents are allowed to make an informed choice as to whether or not they decide to participate. If patient is transported the parents will be supplied with a copy of the consent form by the transport team and then contacted directly by an Investigator or when they arrive to our NICU.

- Provide the consent form in person, give prospective subject sufficient time to review the consent form and discuss with friends/family.
- Consent forms will also be given to the parents by the neonatology transport team and contacted directly by an Investigator.

**8) Procedures Involved**

This is a randomized double blind placebo controlled trial of newborns with neonatal encephalopathy undergoing our standard clinical protocol of whole body cooling. We will approach the parents of eligible infants, describe the study to them, and ask if they want their baby to participate in the study. Infants will be randomized by UCDMC pharmacy to receive cooling with placebo (control arm, n=21) or cooling with topiramate (study arm, n=21). At UC Davis, whole body cooling is a standard treatment for all infants with neonatal encephalopathy.

Active cooling will begin as soon as an infant is admitted to our NICU, using whole body cooling with a goal core temperature of 33.5 degrees Celsius and will be continued for 72 hours. Subject temperature will be monitored continuously using a rectal temperature probe and skin integrity is monitored closely with frequent turning of the

infant. After 72h of cooling, babies are slowly rewarming back to normal body temperature over a period of 12h.

Infants assigned to the topiramate group will receive 5mg/kg of topiramate daily enterally for a total of 5 doses. This is the minimum therapeutic dose of topiramate for infants. The first dose will be administered on the day of enrollment and will continue through and after rewarming. The duration of drug administration was chosen to encompass the cooling period as well as a brief period after rewarming is complete as this is a period where some infants develop seizures and display more signs of neurological damage. The control group will receive a placebo instead of topiramate. Pharmacy will prepare and send to NICU the placebo or study drug solutions in a way to be similar in appearance and volume. Initiation of cooling will not be delayed, but families will be approached for consent as soon as possible after cooling has started.

The cooling protocol includes a range of laboratory evaluations which will be carried out irrespective of whether the patient is enrolled in the study. These include: complete blood count, PTT/INR, DIC panel, complete metabolic panel, ammonia, lactate, troponin-I, CK panel, blood gas, and urinalysis at the initiation of cooling and then every 24h until rewarming is complete (unless the Attending Neonatologist decides that more frequent or less reassessments are needed clinically). Blood gases, blood glucose and ionized calcium levels are measured at the initiation of cooling and then every 6h until rewarming is complete. Once labs have normalized per the discretion of the covering Attending some of these labs may be discontinued. These lab values will provide important data of the severity of each infant's hypoxic-ischemic insult and for patient safety monitoring including information on liver function, kidney function, ammonia toxicity, metabolic status, and acidosis. Enrollment in the study will not change the frequency of these assessments.

A single channel EEG recording (an amplitude EEG, aEEG) or continuous video EEG is recorded continuously on all patients until rewarming is complete. This method measures the degree of encephalopathy and detects seizures.

The Pediatric Neurology service is by protocol consulted on all cooling patients. They will evaluate the infant and determine a neonatal encephalopathy score daily under the supervision of our Pediatric Neurologists. The presence of clinical seizures will be noted based on review of the bedside aEEG or cEEG. The aEEG/cEEG data will be reviewed in 3 hour increments and document the time when the voltages on the aEEG/cEEG first return to normal. The aEEG/cEEG is used throughout the cooling phase and is generally discontinued after rewarming is completed but may be continued longer for abnormal tracings such as seizures at the discretion of the Neonatology Attending. In addition, the Attending Pediatric Neurologist will assess quality of movements, posture, reflexes, and muscular tone, each infant's neurologic status will be categorized as normal (completely normal neurologic status), unspecific signs (eg, asymmetric muscle tone or reflexes) or abnormal with lack of reflexes and bilateral muscular hypotonia or hypertonia.

Additional tests in infants enrolled in this research study include: serum UCHL1 and urine levels of S100β, both will be measured at enrollment, at the start of rewarming, and at one-week of life. Topiramate trough drug levels will be collected 24 hours after the first, third, and fifth doses. The drug levels will be run by the UCDMC laboratory. These

are the only additional laboratory assessment that study infants will receive as a result of taking part in the study.

All infants on the cooling protocol, irrespective of the research study, will have an MRI with spectroscopy on day 5-7 of life. For this study, these images will be read by a single radiologist, our collaborator Dr. Bobinski of Neuroradiology. The reporting of MRI and MRS results will be standardized in conjunction with Dr. Bobinski to create a more consistent scoring method.

Following discharge, each infant will receive long-term developmental follow-up through the MIND clinic our High Risk Infant follow-up clinic. Infants will be seen at approximately 9, 18, and 27 months. The infants will have standardized Bayley Scale of Infant Development (BSID) III neurodevelopmental screening at these clinic follow-ups supervised by Dr. Catherine Rottkamp.

The BSID-III contains 3 domains: cognitive, language (receptive and expressive communication), and motor (fine and gross motor). The cognitive scale includes items that assess sensory perceptual development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing. To allow comparison of results from the 3 domains, a composite score is calculated for each domain (mean, 100). A composite score below -2 SD (<70) is considered a severe delay for all domains. A Pediatrician will assess the quality of movements, posture, reflexes, and muscular tone at each clinic visit. Each infant's neurologic status will be categorized as normal gait and walking, unspecific neurological signs (eg, asymmetric muscle tone or reflexes, muscular hypotonia), or abnormal with upper and/or lower extremities muscular hypertonia (signs of cerebral palsy (CP) present).

## 9) Data and/or Specimen Management and Confidentiality

### Power Calculation

Our primary hypothesis is that topiramate will reduce the frequency of early seizures (i.e. before hospital discharge). From our current data, 64% of infants have seizures prior to hospital discharge; a sample size of 42 will have an 80% chance of detecting a reduction of seizure rate by 2/3 with a p-value of 0.05.

### Statistical Methods

Our primary outcome is that seizures before hospital discharge will be significantly reduced in the topiramate group compared to the controls. This will be assessed by nominal logistic regression with the presence or absence of seizures as the nominal dependent variable, and treatment group (topiramate or control) as an independent variable. Other independent variables will include those that are unbalanced between the treatment groups at randomization, and factors that could affect the risk of seizures (these would include neonatal encephalopathy score at study entry, time to initiation of cooling (< or ≥ 3h), gender etc).

The effect of treatment assignment on neonatal encephalopathy score (measured daily) will be assessed by repeated measures ANOVA with neonatal encephalopathy score as the dependent variable, time and treatment assignment as the independent variable, and addition independent variables included as appropriate (see above). Time to normalization of aEEG/cEEG in the two different groups will be assessed by Kaplan-

Meier analysis. The effect of treatment on S100ß levels in the urine or UHCL1 in the blood and on other markers of tissue injury will be compared using ANOVA (for outcomes measured once) and by repeated measures ANOVA for those measured on more than one occasion, at predetermined times.

Effect of treatment assignment of development assessments will be assessed individually at the 9m, 18m and 27m examinations.

All tests will be considered significant at $p<0.05$. Where necessary, Tukey-Kramer's test will be used to account for multiple comparisons

**Data Specimen/Management**

Data specimens will be stored in the NICU and numerically coded, only those who are involved with this study will have access to the specimens. The specimens will only be stored for the duration of the study and thereafter discarded.

**10) Data and/or Specimen Banking**

There is no plan for specimen or tissue banking in the future.

**11) Provisions to Monitor the Data to Ensure the Safety of Subjects**

To monitor the safety of each newborn we will track the following variables closely during the intervention: blood gases, blood pressure (hypotensive episodes and required interventions), evidence of seizure activity, and serum topiramate levels. This study is only applicable to newborns with neonatal encephalopathy admitted to the NICU at UC Davis for cooling therapy. Neonatal encephalopathy is a life threatening disease with 30% chance of death and 64% chance of seizures during the neonatal period. These patients receive 24 hours daily continuous extremely close physiological and biochemical monitoring based on their underlying disease state.

A Data Safety Monitoring Committee (DSMC) will be utilized for this study. A report will be sent to the chairman of the DSMC every 6 months. He will share this with the other members and meetings will be carried out either by e-mail or face-to-face as the chairman sees fit. The DSMC will remain blinded to study assignation, but will receive summary data for every patient including which agent the patient received (designated as "Study drug A" or "Study drug B"), their short term outcome (incidence of seizures and survival to hospital discharge) and the number of doses of sodium bicarbonate and bronchodilators they received (in order to assess for an increased need for these medications). If the DSMC identifies any trend ($P<0.1$) towards more seizures, reduced survival, an increased need for sodium bicarbonate or bronchodilators they will be allowed to unblind themselves. If the trend is for increased short term need for sodium bicarbonate or bronchodilators, decreased survival or increased seizures in the topiramate group they will be allowed to stop the trial if they wish. However, if the trend favors topiramate over placebo, the DSMC will be expected to allow the trial to continue.

Below are the list and qualifications of DSMC Members: Francis Poulain (Neonatology Attending), Sandra Ellingson (Neonatal Nurse Practitioner), and Andrew Lee (Clinical Pharmacist).

This protocol has risk category 2; namely "research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects." As such we have developed an adverse event grading scale that is detailed below:

1. Adverse Event (AE) Grading and Attribution Scale

If adverse events should occur, they will be assessed using the following grading scale:

0= No adverse event or within normal limits
1= Mild adverse event
2= Moderate adverse event
3= Severe and undesirable adverse event
4= Life-threatening or disabling adverse event
5= Death caused by adverse event

Should adverse events occur, the following Attribution scale will be used to determine the relationship of the adverse event to the study.

- *Unrelated* - AE is clearly not related to the study procedure /intervention/-agent
- *Unlikely* - Relationship to the study procedure/intervention/agent appears to be remote because the factors described with "Probable" and "possible" classification are missing and other factors suggest an alternative etiology exists; such as environmental factors, including common infectious diseases.
- *Possible* - One or more of the above factors suggest a possible relationship to the use of the study procedure/intervention/agent, but other etiologies seem equally or more likely.
- *Probable* - Relationship to the study procedure/intervention/agent seems probable because of such factors as a clear temporal association with the interaction or scanning process; lack of alternative explanations for the experience; or other factors.
- *Definite* - AE is clearly related to the study procedure /intervention/agent.

2. Plan for Unanticipated AE and SAE Reporting

Any serious or unsuspected adverse events will be reported to the Data Safety Monitor Committee (DSMC) and the IRB within 72 hours of the occurrence, or immediately if the event is fatal or life threatening.

3. A Plan for Annual Reporting of AEs

The Principal Investigator will provide an annual patient safety progress report to the IRB, and a twice annual report to the DSMC.

4. Plan for Safety Review

This study will be reviewed by an independent data safety monitoring committee. The committee DSMC (as described above) will review recruitment, safety and efficacy

data every 6 months. In addition, the chair will receive copies of all adverse events and may call an additional meeting, based on the reports received.

The responsibilities of this monitor will include:

- Periodic analysis of the safety of the experimental therapy.
- Review the research protocol, all informed consent documents, and plans for data and safety analysis.
- Evaluate the progress of the intervention, including periodic assessment of data quality and timeliness of data entry, participant recruitment, accrual and retention, and any other factors that may affect the study outcome.
- Review any factors external to the study when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the trial.

**12) Withdrawal of Subjects**

Babies will be ineligible if they have major congenital abnormalities. If the baby had a proven (i.e. electrically confirmed seizure) prior to enrollment they would not be eligible for the study. If a seizure occurred after enrollment/ randomization but before the first dose of study medication the protocol would continue based on the intention to treat. Treatment of seizures will be guided by our Pediatric Neurologists (who will be unaware of treatment assignment). Currently we do not use topiramate for treatment of seizures, and do not intend to change our management of seizures in the foreseeable future. Our first line treatment is phenobarbital, second line is levetiracetam, and the third line treatment is ativan. So, any baby who developed seizures during the protocol would receive our current standard of care, but continue to be in the study. The study protocol will not change the management of seizures should they occur. Once enrolled, a baby would not be withdrawn because of seizures (irrespective of number). We would manage these seizures according to our current clinical practice (see above). Although our primary endpoint (seizures) has been met, we would continue to collect data on secondary endpoints and on safety measures. Patients with renal deficiency (creatinine >2 mg/dL) and liver failure (ammonia >100mcmol/L) will not be eligible for the study.

**13) Risks to Subjects**

Newborns with neonatal encephalopathy are very vulnerable. Given the high risk of lifelong neurologic injury and the low risk of the proposed intervention, the risk to benefit ratio of this study is reasonable. Every effort will be made to ensure that the infants receive excellent care and that the parents of the infants fully understand the benefit/risk of the study. Topiramate has been extensively used to treat variety of neurological diseases including seizures in adults, children, and infants. It is a widely used drug with minimal side effects. In adults, topiramate can cause side effects not likely to be obvious in neonates (e.g. paresthesias, dizziness, fatigue, drowsiness, depression, coordination problems, nausea, and difficulty concentrating). These should not be a problem in study infants as babies who receive whole body cooling are routinely sedated with morphine, and any additional sedative effect from topiramate is likely to be minor. Babies who receive whole body cooling are NPO so the possible side effect of nausea by topiramate should be be minimized.

Pharmacological, pharmacokinetic, and therapeutic studies of chronic administration of topiramate have been conducted to determine its effective dose and to demonstrate its safety in newborn infants (2,4,5). We propose the use of the minimum therapeutic dose of 5 mg/kg/day topiramate for 5 days. However even side effects associated with long term (months) administration of topiramate to infants appear to be minimal. In this study, the serum level of the drug will be monitored in addition to arterial blood gases, blood pressure, and clinical evidence of seizure for any possible side effects. Several studies have used topiramate for treatment of epilepsy or neonatal encephalopathy in infants. In a recent large double-blind placebo controlled prospective study of different doses of topiramate as an adjunctive therapy to conventional antiepileptic drugs in infants a 10% increased rate of fever, diarrhea, vomiting, weight decrease, and viral infection was reported (15). These side effects were dose related and occurred only in infants treated with a higher dose (25 mg/kg/day) of topiramate.

Adverse effects of topiramate administration in this age and population of infants that are not published but have been reported to FDA include: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and bronchospasm. An increased risk for infections (any topiramate dose 12%, placebo 0%). Topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). Monitoring of creatinine, BUN, potassium, and urine output is the standard of care in all patients with neonatal encephalopathy. The risk of viral infections is unlikely given the short duration of therapy. Many infants receiving whole body cooling may require mechanical ventilation due to their underlying disease so bronchospasm is unlikely, and easily treatable should it occur.

One concern on the use of topiramate is the potential to produce metabolic acidosis. From the data of Filippi (2010), although there were no significant effects of topiramate on metabolic acidosis, there was the suggestion in a post-hoc sub-group analysis that topiramate might increase metabolic acidosis in infants receiving deep hypothermia (cooled to 30-33 degrees Celsius) but not in those with moderate hypothermia. As we will be using moderate (not deep hypothermia) we do not foresee this as a problem. However, all infants undergoing cooling will have monitoring of their blood gases, and the detection of acidosis (especially metabolic acidosis) is common and easily treatable-sodium bicarbonate. Should this become a problem, we will therefore, be able to identify it early and respond to it promptly.

For severe adverse events, the drug will be discontinued and clinical intervention will be carried out. Any serious adverse events will be reported to the IRB immediately.

We will prospectively collect data on the number of doses of sodium bicarbonate each baby receives whilst receiving topiramate (or placebo), and the total number of doses of sodium bicarbonate received during their entire hospitalization. We will do the same for the number of doses of bronchodilators (for bronchospasm) the subjects receive. This information will be provided to the DSMC every 6 months for their review.

Potential side effects relevant to the population of this study are also described in lay terms in the informed consent form.

We have enough theoretical and experimental evidence to believe that the benefit of using topiramate in this group of patient outweighs the risk.

Increased risk of brain injury can be detected by measuring the level of S-100 and UCHL1 in the urine/blood respectively in both groups of infants. Neurological examination at 18 month will identify infants in need of further follow up and/or intervention.

Therefore the risk-benefit ratio of this study is reasonable.

**14) Potential Benefits to Subjects**

Topiramate has been successfully used for treatment of epilepsy in infants, and has a good safety record for newborns with neonatal encephalopathy treated with whole body cooling. We have enough theoretical and experimental evidence to believe that the benefit of using topiramate in this group of patient outweighs the risk. There is potential benefit in using the drug for prevention of epilepsy and neurodevelopmental delay in these infants. Increased risk of brain injury can be detected by measuring the levels of S100ß levels in urine and UCHL1 in serum in both groups of infants. Neurological examination at 18 month will identify infants in need of further follow up and/or intervention. The risk-benefit ratio of this study is reasonable.

**15) Multi-Site Research – N/A**

**16) Community-Based Participatory Research – N/A**

**17) Sharing of Results with Subjects – N/A**

**18) Prior Approvals**

This study was previously approved by the IRB in 2013 yet due to funding was placed on hold – we are currently submitting for reapproval. The protocol/plan/aim/benefits/risks all remain the same.

*IND Number: 116892*

**19) Provisions to Protect the Privacy Interests of Subjects**

Patients within the NICU will be approached with full disclosure that non-participation is a viable option, families will be asked if they wish to be contacted, etc.

**20) Compensation for Research-Related Injury**

No compensation will be provided to subjects or guardians of those subjects.

**21) Economic Burden to Subjects**

There will be no cost to subjects.

**22) Drugs or Devices**

*If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

☒ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☐ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

**23)** ClinicalTrials.gov **– Registration has been completed**

FDAAA 801 establishes penalties for Responsible Parties who fail to comply with ClinicalTrials.gov registration or results submission requirements. **Penalties include civil monetary penalties and, for federally funded studies, the withholding of grant funds.**

**Section 1: NIH Funded Studies**

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

| Yes | |
|---|---|
| ☐ | This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.) |
| ☐ | One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. |

**Section 2: Studies subject to FDA jurisdiction**

If yes to ANY the study must be registered on Clinicaltrials.gov.

| Yes | |
|---|---|
| ☐ | This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes. |
| ☐ | This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act. |
| ☐ | This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act. |

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

**Section 3: Publishing the results**

If yes to BOTH the study must be registered on Clinicaltrials.gov.

| Yes | |
|---|---|
| ☒ | This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome. |

| | |
|---|---|
| ☒ | The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations. |

This requirement includes studies of behavioral interventions.

**Section 4: Registration on Clinicaltrials.gov is not required**

| Yes | |
|---|---|
| ☐ | I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research. |

**24) Criteria for 10 Year Approval**

If yes to all items below this research may qualify for a 10-year approval period.

| Yes | |
|---|---|
| ☐ | This research involves no more than minimal risk. |
| ☒ | This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract. |
| ☐ | This research is not subject to FDA jurisdiction. |
| ☒ | This research does not include prisoners as participants. |
| ☐ | This research is not subject to SCRO oversight. |
| ☐ | This research is not subject to oversight by the Research Advisory Panel of California (RAP of C). |
| ☐ | This research does not involve identifiable information held by the State of California Department or Agency |
| ☒ | No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study. |