Compare

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-23365
Status: Approved
Initial Submit Date: 6/10/2008
Approval Period: 11/5/2019 - 11/4/2020

Section Aa: Title & PI

A1. Main Title

COMPASSIONATE USE OF AN INTRAVENOUS FAT EMULSION COMPRISED OF FISH OIL IN THE TREATMENT OF PARENTERAL NUTRITION INDUCED LIVER INJURY IN CHILDREN

A2. Principal Investigator

Name:	MURALIDHAR PREMKUMAR	Phone:	832-826-7980
Id:	159712	Fax:	832-825-2799
Department:	PEDIATRICS: NEWBORN	Email:	premkuma@bcm.edu
Center:		Mail Stn:	BCM320

A3. Administrative Contact

Name:	ALICIA WRIGHT	Phone:	832-826-1380
Id:	201812	Fax:	
		Email:	aw19@bcm.tmc.edu
		Mail Stn:	BCM320

A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

A4. Co-Investigators

Name:	KRISTIN WHITFIELD VAN BUREN	Phone:	832-822-3616
Id:	041311	Fax:	832-825-3633
Department:	PEDIATRICS: GASTROENTEROLOGY	Email:	klw@bcm.tmc.edu
Center:		Mail Stn:	BCM320
Name:	JOHN DAVID HOOVER	Phone:	832-826-1309
Id:	156657	Fax:	
Department:	PEDIATRICS: NEWBORN	Email:	hoover@bcm.tmc.edu
Center:		Mail Stn:	BCM320
Name:	AMY HAIR	Phone:	832-826-1309
Id:	167379	Fax:	
Department:	PEDIATRICS: NEWBORN	Email:	abhair@texaschildrens.org
Center:		Mail Stn:	BCM320
Name:	LAURA GOLLINS	Phone:	832-826-3639

Id:	197398	Fax:	
Department:	PEDIATRICS: NEWBORN	Email:	gollins@bcm.tmc.edu
Center:		Mail Stn:	BCM320
Name:	LISA OWENS	Phone:	832-826-1380
Id:	670300	Fax:	
Department:	PEDIATRICS: NEWBORN	Email:	lo1@bcm.tmc.edu
Center:		Mail Stn:	BCM320

A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

CNRC: Children's Nutrition Research Center
TCH: Texas Children's Hospital
TCH: Texas Children's Hospital General Clinical Research Center
TCH: Texas Children¿s Hospital The Woodlands
Texas Children's Hospital- Women's Pavilion

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Yes

A9. ClinicalTrails.gov Registration

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Background Section

Parenteral nutrition (PN) provides intravenous nutritional supplementation for patients unable to absorb adequate enteral nutrients secondary to insufficient intestinal length or function. PN contains the macronutrient building blocks of the human diet in their most elemental forms (amino acids and dextrose) and is commonly administered with a lipid emulsion to avoid essential fatty acid deficiency and to provide a calorically dense source of non-protein calories. In addition, PN contains the essential micronutrients (electrolytes, trace elements, and vitamins) to provide an optimal nutritional regimen. Before the development of PN in the late 1960¿s, patients with insufficient gastrointestinal absorptive function commonly died of starvation and subsequent complications of malnutrition (1, 2). Today, more than 30,000 patients are permanently dependent on parenteral nutrition for survival. However, PN continues to be associated with hepatic injury that occurs at an unpredictable rate and includes both biochemical, i.e., elevated serum aminotransferase and alkaline phosphatase, and histologic alterations such as steatosis, steatohepatitis, lipidosis, cholestasis, fibrosis, and cirrhosis (3, 4). These abnormalities, which may worsen with the duration of PN administration, is more prevalent in the pediatric population. Additional risk factors for this condition include prematurity, low birth weight, long-term use of PN, the lack of concomitant enteral intake, sepsis, and multiple operative procedures (5).

Although the pathological features of PN-induced liver injury have been well described, the etiology, prevention, and treatment of this complication are not well understood. Multiple hypotheses exist to explain the pathogenesis of PN-

induced liver injury including altered gut hormonal profiles (6), the propensity for bacterial translocation in the absence of enteral intake (7, 8), intestinal stasis resulting in the reduced clearance of hepatotoxic bile acids (8), and direct deficiencies or toxic components of the PN solution itself resulting in excessive glucose calorie uptake, excessive lipid infusion, or nutritional deficiencies such as essential fatty acid deficiency (9-11). None of these theories has been confirmed consistently. The etiology of PN-associated hepatotoxicity is currently considered multifactorial. Available treatment options for this disease process are limited and have achieved moderate success at best. Care of the PN-dependent patient is focused on gradually increasing enteral caloric intake as the residual bowel adapts allowing PN to be discontinued (12). In fact, it has been shown both experimentally and clinically that partial enteral nutrition, when tolerated, helps to protect against the development of PN-associated liver injury (13-15). In severe cases of refractory hepatic failure, liver transplantation with or without accompanying small bowel transplantation remains the only treatment option.

The mechanism of clearance of omega-3 fatty acid containing lipid emulsions is unknown, but appears to be largely independent of the pathways identified above (17). Furthermore, omega-3 fatty acid solutions have been shown to decrease de novo lipogenesis (18), prevent or attenuate PN-induced hepatosteatosis in rats (19) and guinea pigs and ameliorate the severity of high-fat diet-induced hepatosteatosis in rats (20). In addition, omega-3 fatty acids can interfere with the arachidonic acid pathway of inflammation (18, 21). They can displace arachidonic acid from tissue fatty acid pools, thereby reducing the availability for eicasanoid-synthesizing enzymes and inflammation (21).

Current experience with Omegaven:

The total number of infants given Omegaven to date is approximately 55 in Boston and 300 in the US in 35 centers. Essentially all but 3 of these centers have given Omegaven using a compassionate use protocol.

Recently, an article by Puder et al from Boston Children¿s Hospital was published in Pediatrics reporting on 18 infants who received Omegaven (22). A copy of his paper is attached in Section S. In brief, time to reversal of cholestasis (conjugated bilirubin less than 2) was 9 wks compared to 44 wks in a group of 21 historical controls. In addition, only 1/18 was found to have biochemical evidence (although not clinical symptoms) of transient essential fatty acid deficiency. In fact, the infant had been off the Omegaven product for 3 weeks when this occurred and it was thought to be more related to low volume enteral feedings, thus the Omegaven was actually restarted to correct the observed deficiency. In general, the available data from Boston is that about 5% of infants will have a brief mild elevation in their tetraene/triene ratio that then resolves. There has been no indication in any patient to stop therapy due to this and no clinical symptoms of fatty acid deficiency. Recent animal data further demonstrate a lack of essential fatty acid use with Omegaven (23). All 5 infants studied to date who received long-term (greater than 2 weeks) Omegaven while on minimal or no enteral feeds at TCH have had no evidence of even mild EFA deficiency when measured. All had triene/tetraene ratios that were normal.

In addition, Dr. Puder has unpublished data showing an overall improvement in bleeding and clotting status on Omegaven. In our experience, there has been no bleeding event or adverse elevation in any clotting parameter after starting Omegaven.

In our current Omegaven study (H-21344), we have completed 14 of the 15 subjects. Of these 14, to date, 12 have resolved (conjugated bilirubin below 2; all are below 0.5 and all but one are off therapy), 2 others have just started receiving the Omegaven therapy, and 1 died. Mean time to resolve = 31 ± 18 days (range = 15 - 77d). Of the first 12 enrolled, all had a peak bilirubin greater than 5 at some point. Six had a peak bilirubin of at least 10 mg/dL. Of these 5 resolved, 1 died of congenital heart defects and preexisting sepsis and the others are currently receiving the Omegaven therapy. Total days of therapy = 307. Total number of infections = 2. Rate of infection = 2/307 = 0.0065. There have been no other complications.

To compare with our chart review data: In the historical controls, infection risk was 37/2700 = 0.0137. Therefore, current frequency of infection (0.0065 as shown above) is 48% of the historical rate. Rate of infection of the current Omegaven group total is 2/11 babies with a positive blood infection vs. 42/66 in chart review (P less than 0.05). Of note is that the data from Boston similarly shows a reduction to about 50% of the baseline infection rate after using Omegaven. In addition, based on historical control data and data from the subjects in H-21344, patients with a conjugated bilirubin >6 mg/dL were highly likely to go on to have a conjugated bilirubin >10 mg/dL. Of those with a conjugated bilirubin greater than 10 mg/dL, deaths from liver related causes from the chart review were 6/19 versus 0/5 so far among those completing the Omegaven course. Overall mortality was 11/66 in chart review versus 1/12 so far on Omegaven. These values are extremely similar to the results from Boston. Mean time of resolution among survivors in our chart review was 48 ± 5d (n=42) vs. 31 ± 18d so far on Omegaven.

In protocol H-21344, we have been monitoring all liver function tests and triglyceride levels. All of these show marked rapid improvement on Omegaven. The tetraene/triene ratio was obtained and as noted above was normal on our 5 infants to date who were not receiving 1-2% of calories from EFA. As noted, the Boston group found no long-term abnormalities in any patients in this level out of over 50 studied to date.

Neurodevelopmental outcome testing is offered at our NICU to all at-risk infants which would include most if not all of these babies. However, as this is a compassionate use, not a controlled trial, and given the population¿s risk factors, it is estimated that nearly 100% of infants will have some developmental delay. There is no method by which this trial can isolate the therapy as contributing to the improvement or worsening of any developmental outcomes. However, given the severe effects of long-term growth failure on developmental outcomes, it is our best judgment that outcomes will be improved.

Once all the subjects have been enrolled in H-21344, there will not be another mechanism for patients to receive Omegaven. After discussions with the BCM Office of Research and the FDA Center for Drug Evaluation and Research, it was determined that a protocol for compassionate use of the investigational drug would be the most appropriate course of action. One of the main changes from H-21344 to this protocol is that the eligibility criteria for conjugated bilirubin is increased from 2 mg/dL to 6 mg/dL based on currently available data that these subjects are most likely to have the most severe consequences from hepatic injury and therefore would receive the most benefit from the Omegaven. It is our best estimate, based on our data and the literature, that infants with a conjugated bilirubin > 6 and likely to need 2 more weeks of TPN have a 35-75% overall mortality risk which is decreased to < 10% with Omegaven. Therefore, while the FDA processes of approving Omegaven are ongoing, we, along with the many other centers in the US using Omegaven wish to continue to offer this on a compassionate use basis. This continuation has the strong support of all representative Baylor clinical services, including neonatology, GI and hepatology and pediatric surgery.

Rationale for cutoff of bilirubin greater than or equal to 6 mg/dL for inclusion criteria:

Upon analysis of the data from the 14 babies in our first Omegaven study (H-21344), 7/14 babies who had direct bilirubins greater to or equal than 6 mg/dL progressed to direct bilirubins greater to or equal than10 mg/dL. Of these, 4 of the 7 were started on Omegaven after the bilirubin reached 10 mg/dL. The remaining 3 were started with bilis greater to or equal than 6 mg/dL but the bilirubin reached 10 mg/dL anyway.

Of the remaining 7 babies who did not reach 10 mg/dL, 4 never reached a bilirubin of 6 mg/dL by virtue of being started on Omegaven at a bilirubin of 2-5 mg/dL. All 4 babies had peak bilirubins of about 5 mg/dL.

The remaining 3 babies were started on Omegaven at bilirubins less than 6 mg/dL and while the bilis did increase, they did not progress to a bilirubin greater than 10 mg/dL due to the intervention. One of these babies was the exemption baby who was enrolled apart from the primary protocol. Another baby who did not reach 10 mg/dL would not have been eligible for Omegaven under this new protocol (due to being advanced to full feeds quickly). Therefore, only one was a case of a baby who was started at a bilirubin greater than 6 mg/dL but did not reach 10 mg/dL. Considering this case along with the 7 babies first mentioned who hit 10 mg/dL indicates that 7/8 babies with a bili greater to or equal than 6 mg/dL progressed to direct bilirubins greater to or equal than10 mg/dL.

In total, 7 of the 10 babies with cholestasis whose bilirubin exceeded 6 mg/dL reached a bilirubin of 10 mg/dL regardless of Omegaven. In contrast 0/4 who were started before hitting 6 mg/dL reached 6 mg/dL.

In the retrospective cholestasis chart review (H-21367), 21/37 infants whose bilirubin greater to or equal than 6 mg/dL ultimately exceeded 10 mg/dL. In contrast, only 21/56 infants whose bilirubin exceeded 4 mg/dL ultimately exceeded 10 mg/dL.

Also, by chi-squared tests, 0/9 babies on Omegaven with a bilirubin greater to or equal than 6 mg/dL died of non-pulmonary causes, compared to 9/37 in the historical review ($p = 0.09$, trending toward statistical significance).

Finally a power point slide attached in Section S (from Teitelbaum, Curr Opinion in Peds, 1997) indicates that all those with bilirubin ~6 mg/dL or above died, thus confirming from the literature our data indicating that a bili that does not exceed 5-6 mg/dL is much more likely to lead to resolution than an infant with a bili greater to or equal than 6 mg/dL.

We conclude that the enrollment criteria of 6 mg/dL and limited or no feeds in our population are consistent with 7/8 babies progressing to a bili greater than 10 mg/dL (i.e., ¿highly likely¿). Babies who have a peak bili of about 5 mg/dL are more likely to recover if feeds are established and maintained. This is the primary basis of establishing the cut-off of 6 mg/dL (and limited feeds) since it is indicative of babies who will reach a bili of 10 mg/dL.

Home Use of Omegaven:

Boston Children's Hospital has seen improvement in over 50 infants who have received Omegaven® long-term (at home) and no negative effects have been seen (Gura et al, 2008). Use in this long-term fashion may delay or prevent the need to do an intestinal transplant related to ongoing liver failure (Gura et al, 2006).

Our expectation is that most subjects will receive the Omegaven® at home for at least 6 months. There is no minimum or maximum length of time for the subject to receive the Omegaven®. In fact, Boston Children¿s Hospital is currently following several children who have received Omegaven® for over 2 years and one child who has received it for almost 5 years.

References for Home Use:

Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP, Arsenault DA, Strijbosch RA, Lopes S, Duggan C, Puder M. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics. 2008 Mar; 121(3):e678-86.

Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrian BR, Puder M. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics. 2006 Jul;118(1):e197-201. Update on 10/5/2018: Omegaven got approved by the FDA on 7/27/18 for use in the pediatric infants with parenteral nutrition-associated cholestasis. However, Omegaven will not be

commercially available until November or December of 2018. Until then it is imperative to keep this IND compassionate use protocol to ensure supply of Omegaven to our patients.

Section D: Purpose and Objectives

To provide a mechanism for critically ill infants with parenteral nutrition (PN) associated cholestasis to receive Omegaven for compassionate use situations for which there are no satisfactory alternative treatments.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:
Both

Age:
Adolescent (13-17 yrs), Child (3-12 yrs), Infant/Toddler (0-36 mos), Premature Infant (<37 weeks gestational age)

Ethnicity:
Asian/Non Vietnamese, Black Or African American, Hispanic Or Latino, Mixed Race Or Ethnicity, White

Primary Language:
Chinese, English, Spanish, Vietnamese

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?
Children

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Each family will have the severity of their child's condition explained to them and the available data regarding the benefit of the novel preparation explained using the preliminary safety and efficacy data from Boston Children's Hospital and TCH. Families will have the potential risks and benefits of the product explained. The lack of long-term follow-up information regarding the effects of Omegaven will be discussed.

Non-English speaking families will be provided with a consent form in their language. Spanish speaking families will have a full-length Spanish consent form. Speakers of other languages will have an approved short consent form downloaded from the IRB website that is used in combination with a translator. In this circumstance, the parent will sign the foreign language Short Consent Form. The PI or Co-Inv Designee will sign the full length English consent form. The translator will sign both the foreign language short consent form and the English consent form. If the translation service was provided by telephone or video-conferencing, the consent forms (both English and foreign language versions) will be faxed to the translator for signature and faxed back to us. Copies of both consent forms will be provided to the parent to keep.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
Yes

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

z.z) ARCHIVED DO NOT USE - Other: Compassionate Use

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

Infants and children who meet the inclusion criteria specified below will be offered the possibility of enrollment.

Inclusion Criteria:

1. Be greater than 10 days old and less than 18 years of age

2. Conjugated bilirubin greater than 2 mg/dL

3. Be expected to require intravenous nutrition for at least an additional 28 days

Exclusion Criteria:

1. Have a congenitally lethal condition (e.g. Trisomy 13).

2. Have clinically severe bleeding not able to be managed with routine measures.

3. Have evidence of a viral hepatitis or primary liver disease as the primary etiology of their cholestasis (except biliary atresia which will be allowed).

4. Have other health problems such that survival is extremely unlikely even if the infant's cholestasis improves.

F2. Procedure

Bottles containing 50 or 100 mL of 10% Omegaven will be purchased from International Pharmacy of Hamburg, Germany. Omegaven is manufactured by Fresenius Kabi AG, Bad Homburg v.d.h, Germany and is formulated as an emulsion from fish oils. The family (or legal guardian) will be billed for it as part of their hospital bill from TCH. Omegaven will be dispensed per TCH policy and procedures for fat emulsions. Details of Omegaven Administration: Therapy with Omegaven will be provided at a dose of 1 gm/kg/day (by continuous infusion) and will be infused intravenously through either a central or peripheral catheter in conjunction with parenteral nutrition. Parenteral fat emulsion (Intralipid) will be administered only if necessary to administer adequate calories during Omegaven therapy. The same standards of care provided to all patients receiving parenteral nutrition solution will be followed.

Ongoing monitoring during therapy related to safety and efficacy: Safety will be assessed using the following outcome variables. First, we will calculate the number (total and daily rate) of bloodstream infections prior to therapy. We will monitor this rate in each baby receiving Omegaven and compare with the previous rate. Currently, the rate of infection in infants receiving Omegaven is about half of the historical control rate at TCH. Second, we will monitor growth rate using weight, length and head circumference growth. Growth will be compared both to the pre-treatment period and the expected rate of growth. We have established and have guidelines for optimal growth targets and management will be targeted on achieving these rates. We will monitor these carefully. For babies in the NICU or Level 2 nurseries, Dr. Premkumar will supervise the nutritional management directly. Infants in the PICU or PCU will be followed by Dr. VanBuren with the critical care staff. This approach has been in place for the current group of 15 infants and growth has been excellent although final calculations are pending. Third, we will monitor infants who are not receiving any enteral feeding at all for more than 4 weeks for any evidence of essential fatty acid (EFA) deficiency. Measurements will be repeated at the end of every 4 weeks that the subject remains without any enteral nutrition intake. Although the exact value suggestive of a deficiency is controversial, usually a level greater than 0.4 is considered evidence of EFA deficiency. This measurement may be made using 0.2 mL of serum in the lab of Dr. William Heird. Samples will be drawn monthly for infants who are NPO and run as a batch in Dr. Heird¿s lab in the CNRC every 6 months. Because data are not available for clinical use, we will include in the consent the possibility of EFA deficiency. We note again that no infant ever treated with Omegaven has ever shown clinical evidence of EFA deficiency, that very transient mild deficiency may occur in about 5% of infants and that there is no clinical intervention we would use in this case or that has ever been given without clinically apparent EFA deficiency. Fourth, we will record and monitor the following laboratory results: triglycerides, conjugated bilirubin, ALT, AST, GGT. Additionally, we will monitor coagulation including PT, PTT , INR, fibrinogen and platelet count prior to initiation and every 4 weeks thereafter. See Attachment Titled "Amendment 2016.doc" for additional details. Finally, with regard to developmental follow-up we will indicate to families that all infants with cholestasis may be at risk for developmental delays and recommend that they be followed. There is no mechanism in place to assure this follow-up occurs for any infants in the TCH nurseries however.

Dose Modification Hypertriglyceridemia: If hypertriglyceridemia develops, defined as serum triglyceride levels > 300 mg/dL, the following will be considered prior to reducing the dose: a) If the level was obtained while the patient was receiving a continuous 24- hour infusion of Omegaven, the total dose should be infused over 20 hours, and a repeat serum triglyceride level obtained prior to resuming the infusion 4 hours later. b) Other sources of hypertriglyceridemia should be considered and addressed (drugs, renal disease) If necessary if the triglycerides continue to remain high despite the aforementioned interventions, a dosage reduction of 25% will be considered.

Duration of Therapy Patients will remain on Omegaven until weaned from PN. In the event that a patient who has been

listed for a liver or liver/intestinal transplant has an organ become available, the participation in this protocol will not preclude them from receiving the transplant. Omegaven will not be administered post transplant.

If the infant no longer is requiring any TPN, then the Omegaven will be stopped regardless of bilirubin. If the bilirubin is less than 2 mg/dL but the child still requires TPN, then the Omegaven will be continued up until the infant no longer requires TPN. The reason for stopping Omegaven when the infant no longer requires TPN is that this would be the only reason many infants would still need IV access and therefore the risk of maintaining IV access only for the medication is likely to exceed the benefit of Omegaven at that point.

Resumption of Omegaven: See Attachment Titled "Amendment 2016.doc" for full details.

Home Use of Omegaven: In order for a subject to receive the Omegaven® at home through the home health care agency, subjects will first be required to be admitted to TCH for 48 hours in initiate the administration of the Omegaven®. This will allow time for observation of any unexpected side effects and for parents to be provided education on home TPN and Omegaven.

If a subject has already received Omegaven® either at TCH or at another hospital, they will not be required to be admitted for the 48 hour inpatient admission prior to starting Omegaven® at home. Parent training will occur during the previous hospital admission and will continue through the TCH Pediatric Intestinal Rehabilitation Clinic.

Education to the parents will be documented as is required for all education to parents at TCH. The education may be provided by the inpatient nursing staff, home health agency nurses, or staff at the TCH Pediatric Intestinal Rehab Clinic.

This population will include infants up to 5 years of age. The Omegaven® dose for home use will be the same as that used while in the hospital: 1 gm/kg/day. As with the inpatient part of the protocol, this is a maximum dose and may be decreased at the discretion of the TCH Pediatric Intestinal Rehabilitation Clinic Team.

Subjects will be billed for the Omegaven® at home just as they are billed for it while hospitalized at TCH. Thus far, we are not aware of any Medicaid rejections of Omegaven® in our population and anticipate that Medicaid will continue to cover the cost for home use.

Outpatient Monitoring: After the initial evaluation by the TCH Pediatric Intestinal Rehabilitation Clinic physicians, subjects will return to the clinic for routine follow-up. Subjects will be asked to return to the clinic every 2 weeks for the first 2 months of treatment. Thereafter, subjects will return to the clinic on a monthly basis, or as directed by the clinic team. Orders for home use of Omegaven® will be signed by the physician at the clinic visits, ensuring that subjects are compliant with study parameters while receiving the treatment drug. It will be explained to the parent/legal guardian that these follow up visits are important and that the study physicians reserve the right to drop the subject for non-compliance because safety measures cannot be adequately monitored.

Routine monitoring done at clinic appointments and at home will be recorded for study purposes and data collection. No blood work will be done for study purposes only. Anthropometrics, new diagnoses, surgical procedures, medications, hospital readmissions, infections, feeding plans (e.g., volume, caloric density, and name of enteral formulas), and other pertinent data will also be recorded for study purposes. The TCH Pediatric Intestinal Rehabilitation Clinic physicians will monitor clinically for signs of an essential fatty acid deficiency and adjust the nutrition strategy as needed.

Lab monitoring will typically be done every week to two weeks at home and at each clinic visit. Typical lab monitoring will include BUN, CO2, creatinine, glucose, serum chloride, serum potassium, serum sodium (Chem 7), serum calcium, serum phosphorus, serum magnesium, triglycerides, CBC: WBC or leukocyte count, WBC differential count, RBC or erythrocyte count, Hct, Hbg, MCV, MCH, MCHC, red cell distribution width (RDW), platelet count, and mean platelet volume (MPV), and a liver panel: ALT, AST, GGT, AP, albumin, total protein, direct bilirubin (conjugated), total bilirubin, lactic acid dehydrogenase (LDH), and prothrombin time (PT).

Routine evaluations done through the home health service will be continued as usual. If the home health team or TCH Pediatric Intestinal Rehabilitation Clinic Team discovers any unexpected problem(s) involving a risk to the subject or others that are potentially liver-related or Omegaven®-related, the study physician and study coordinator will be immediately notified so that a report can be sent to the IRB and the FDA within 24 hours.

If a subject is consented under the ¿home use¿ consent form and is subsequently readmitted to TCH, the Omegaven and monitoring will continue as discussed for the inpatient use and a specific inpatient use consent form is not necessary. All subjects who are receiving Omegaven on home-use protocol, if re-admitted to the hospital will be re-consented for in-patient use of Omegaven, irrespective of the duration of discharge from the hospital.

Exception Status: If a subject does not meet inclusion criteria, data will still be collected however it will not be included as part of our overall data in terms of time to resolution. Data will still be reported to the FDA in our annual report to them and noted as a exception.

Data from 66 non-Omegaven patients (January 1, 2006 and April 1, 2007) will be recorded to serve as historical controls. Data will be coded to decrease the risk of loss of confidentiality. Codes to identify patients will be kept separate from the rest of the data files, all of which will be maintained in password protected servers and locked file cabinets. Data will include: date of birth, date of admit, birth weight, birth length, birth head circumference, gestational age, admit weight,

admit length, admit head circumference, gender, race/ethnicity, singleton or multiple birth status, medical and surgical history, type and volume of feeds, age at critical time points of feeds including first feeds, full feeds (defined as 150 ml/kg), maximum volume feeds if

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 376 Worldwide: 376

Please indicate why you chose the sample size proposed:

We propose to enroll all eligible subjects that meet study criteria over the next year. We expect this to be 30 subjects per year based on recent admissions. We have requested the sample size to be increased to 376 subjects. This is based on our previous enrollments. In the past we have enrolled 25-35 subjects every year, hence we have increased the sample size from 346 to 376.

While awaiting the commercial availability of Omegaven following its approval by the FDA we will continue enrollment (both inpatient and home use including an increase in referrals). Hence, we have decided to extend the enrollment to 376 subjects, including the 66 additional subjects requested by the FDA for historical control purposes.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

We will be calculating for outcome analysis:

1. Total days of TPN

2. Maximum conjugated bilirubin

3. Time to resolution of bilirubin or death/transplant

4. Positive blood cultures

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

Potential Risk of Omegaven Treatment

No complications from Omegaven have occurred in any of the approximately 1,000 infants who have received it to date.

Omegaven has been studied in animal pre-clinical models as well as Phase I, II, III, and post marketing human trials in both Europe and Asia. Prolonged bleeding time and an inhibited platelet aggregation can occur. It should not be administered to patients known to be allergic to fish or egg protein.

Contraindications to Omegaven include the following:

Impaired lipid metabolism (severe), severe hemorrhagic disorders with active uncontrolled clinical bleeding, unstable diabetes mellitus, collapse and shock, stroke/embolism, recent cardiac infarction, or undefined coma status.

Side effects:

The infusion of Omegaven can lead to a prolonged bleeding time and an inhibited platelet aggregation. Severe clinically apparent bleeding that was not present before the use of Omegaven such that blood products or surgical intervention are needed would be considered a serious adverse event. Changes in coagulation profile that required intervention not needed prior to the use of Omegaven or a serum triglyceride level that exceeded 400 mg/dL that did not exceed that value before Omegaven would be considered serious adverse effects.

The administration of Omegaven should be stopped or reduced if there is a marked increased in blood glucose levels during the Omegaven infusion.

Overdose: In the event of an overdose of Omegaven, there is a risk of developing fat overload syndrome that may occur

when the triglyceride level rises acutely as a result of too rapid a rate of infusion, or chronically at high infusion rates in associated with a change in the patient¿s clinical condition (e.g., renal dysfunction, sepsis). In such cases, the infusion should be stopped or, if necessary, continued at a reduced dose.

Metabolic acidosis has occurred in patients receiving Omegaven at excessive doses without simultaneous administration of dextrose.

This study will be monitored by an independent data safety monitoring board (DSMB). The DSMB will review recruitment, safety and efficacy data every year. 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 board will include: 1. Periodic analysis of the success and safety of the experimental therapy. Success will be measured by each patient's improvement in biochemical markers and avoidance of end stage liver failure. 2. Review the research protocol, all informed consent documents, and plans for data and safety analysis. 3. 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. 4. 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. 5. Ensure the confidentiality of the trial data.

The DSMB will be able to contact the investigators at any time by telephone or pager to facilitate adequate feedback of information to medical decision-makers. This will ensure that research felt to involve excessive risk in relation to anticipated benefits is terminated appropriately. To prevent potential or real conflicts of interest, if the research procedure is deemed by the DSMB to involve excessive risk in relation to anticipated benefits, the investigators will be contacted by phone or pager. The research will then be suspended pending further investigation, or terminated at the suggestion of the Board. Membership of the DSMB will include:

Robert Shulman, MD (DSMB Chair, BCM); Mark Puder, MD (Boston Children's Hospital); Kathleen Gura (Boston Children's Hospital); and Stephanie Abrams, MD (BCM)

The DSMB will be able to contact the investigators at any time by telephone or pager to facilitate adequate feedback of information to medical decision-makers. This will ensure that research felt to involve excessive risk in relation to anticipated benefits is terminated appropriately. To prevent potential or real conflicts of interest, if the research procedure is deemed by the DSMB to involve excessive risk in relation to anticipated benefits, the investigators will be contacted by phone or pager. The research will then be suspended pending further investigation, or terminated at the suggestion of the Board.

There is a small risk of loss of confidentiality. However, study personnel will make every effort to minimize this risk by only using secure servers for data analysis. All protected health information will be coded.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?
No

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?
No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.
Omegaven may be effective in stabilizing or reversing hepatic injury associated with the use of parenteral nutrition. It may allow the patient to continue to receive the majority of his/her caloric intake from parenteral nutrition while advancing on enteral nutrition or awaiting liver or liver/intestinal transplant.

In addition, mortality from hepatic injury has been estimated to be 40-75% among this population using currently available lipid preparations (Intralipid). Currently, the rate of infection in infants receiving Omegaven is about half of the historical control rate at TCH.

There are no benefits for historical control subjects.

Describe potential benefit(s) to society of the planned work.
This compassionate use protocol provides a mechanism for neonatologists to better understand the efficacy of Omegaven for the treatment of a serious and life-threatening illness (parenteral nutrition-associated cholestasis) for which there are no satisfactory alternative treatments.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

Anticipated benefits outweigh the potential risks. The risk: benefit ratio is favorable for subjects.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

Yes

Please describe the portion of the research for which a waiver is required. (Example: chart review to determine subject eligibility)

Yes. A waiver of consent is required for the subjects in the subgroup of historical controls in the TCH NICU prior to the start of Omegaven in the NICU. Note that all of the data that will be reviewed have already been published in the peer-reviewed literature

Explain why the research and the use or disclosure of protected health information involves no more than minimal risk (including privacy risks) to the individuals.

This observational chart review project only seeks to evaluate clinical management practices for infants with TPN-associated cholestasis in the TCH NICU prior to the start of Omegaven in the unit. All data will be obtained from the patient's medical record. There are no interventions. This protocol involves only minimal risk to individuals. A waiver of consent would not in any way adversely affect the privacy rights and the welfare of the individuals because of the observational nature of the study and because all data will be coded as described in Section K.

Explain why the waiver will not adversely affect the privacy rights and the welfare of the research subjects.

In order to evaluate the presence of TPN-associated cholestasis and subsequent treatment in this subgroup, we must have access to the patient's medical record to obtain the clinical labs, medical history, nutritional intake, and medications.

In addition, we are evaluating the effectiveness of clinical management programs in the NICU, not nutritional success of individual infants. Because of the inherent lack of risk associated with this protocol, the need to include a wide cross-section of all infants in the NICU, and the goal of quality assessment of nutritional programs for TPN-associated cholestasis rather than individual patient outcomes, we believe a waiver of consent is appropriate.

Furthermore, all data will be coded. Codes will be destroyed at the earliest opportunity after the FDA has reviewed the data.

Explain why the research could not practicably be conducted without the waiver and could not practicably be conducted without access to and use of the protected health information.

These subjects are all from TCH NICU hospitalizations from 2006-2007. Scientific validity would be compromised if consent was required due to subjects lost to follow up. Reliable contact information is lacking and a follow-up process for these patients and families is not in place.

Describe how an adequate plan exists in order to protect identifiers from improper use and disclosure.

Patient information will only be accessed by study staff of this protocol. All patient information and identifiers will be stored on a locked computer on a secured BCM server.

Describe how an adequate plan exists in order to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

All patient identifiers and information will be destroyed at the earliest possible date. In regards to data shared with the FDA, all data will be coded. Codes will be destroyed at the earliest opportunity after the FDA has reviewed the data.

Describe how adequate written assurances exist in order to ensure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Patient information and identifiers will be protected in accordance with the law. Information will not be shared with any third party that has not been approved by the BCM IRB.

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

No

Specific information concerning drug abuse:

No

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Other:
No

Will additional pertinent information be provided to subjects after participation?
Yes

If Yes, explain how subjects will be provided additional pertinent information after participation.
Parents of subjects who are currently receiving Omegaven will be provided with any new pertinent information in a timely manner. All information will be provided in person (first choice) or by phone or letter, depending on the parent/guardian's availability. If subjects have completed the Omegaven treatment, parents will not be provided additional pertinent information unless it refers to a previously unknown side effect that may affect their child.

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
No

J2. Consent Procedures

Who will recruit subjects for this study?
PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Legal and Ethics Requirements: This study is being conducted under a FDA Investigational New Drug Application using an IND originally obtained by Dr. Abrams and since transferred to Dr. Premkumar (IND # 102,843). All study procedures will be performed under this IND number.

The Investigators will be responsible for obtaining an Informed Consent signed by each patient or his/her legally authorized representative prior to his/her participation in the study in accordance with the Code of Federal Regulations, Title 21, Part 50.20. Informed Consent will be obtained from a patient or his/her legally authorized representative after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc. have been provided by the Investigator or designee, both verbally and in writing. The person who signed the consent will be given a copy of the signed consent form. The lack of long-term follow-up information regarding the effects of Omegaven will be discussed.

Non-English speaking families will be provided with a consent form in their language. Spanish speaking families will have a full-length Spanish consent form. Speakers of other languages will have an approved short consent form downloaded from the IRB website that is used in combination with a translator. In this circumstance, the parent will sign the foreign language Short Consent Form. The PI or Co-Inv Designee will sign the full length English consent form. The translator will sign both the foreign language short consent form and the English consent form. If the translation service was provided by telephone or video-conferencing, the consent forms (both English and foreign language versions) will be faxed to the translator for signature and faxed back to us. Copies of both consent forms will be provided to the parent to keep.

For any exception patients that are included with specific IRB permission, the use of Omegaven will be explained to the family as with all subjects; however, special mention will be made of the patient's exception status and why we are using Omegaven anyway even though he/she doesn't meet the inclusion criteria.

A waiver of consent is requested for subjects in the historical control subgroup only. Details about this waiver are attached in Section S.

Are foreign language consent forms required for this protocol?
Yes

Which of the following ways will you document informed consent in languages other than English?
Short-Form consent documents

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
Yes

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?
Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes

Specific information concerning alcohol abuse:
No

Specific information concerning drug abuse:
No

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):

No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Other:
No

At what institution will the physical research data be kept?
Texas Children's Hospital - Pavilion for Women

How will such physical research data be secured?
physical data will be kept in locked storage cabinets and closely monitored.

At what institution will the electronic research data be kept?
PHI will be kept on password protected, locked databases that may be accessed on a Baylor College of Medicine secured server.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes

Such electronic research data will be secured via Other:
No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
Coded information will be shared with the DSMB utilizing secure email. No patient identifiers will be available.

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
Subject identifiers will be destroyed at the earliest opportunity after the FDA has reviewed all data submitted to them and does not request additional data.

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
Texas Children's Hospital will obtain the product from Germany for inpatient use. Families will be billed for the cost of the medication based on an approval for this obtained via the FDA. Families will be informed of the costs. All other costs routinely associated with parenteral nutrition will continue as always to be the responsibility of the patient.

Subjects will be billed for the Omegaven® at home just as they are billed for it while hospitalized at TCH. Thus far, we are not aware of any Medicaid rejections of Omegaven® in our population and anticipate that Medicaid will continue to cover the cost for home use. Families will be informed of the costs. All other costs routinely associated with parenteral nutrition will continue as always to be the responsibility of the patient. Baylor College of Medicine and Texas Children¿s Hospital will not profit from this study.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

SAMPLE: Serum

What is the purpose of the sample collection?

Measurement of triene/tetraene level to assess essential fatty acid deficiency

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

After every 4 weeks that the subject remains without any enteral nutrition intake at all while hospitalized, 0.5 mL of blood will be taken for triene:tetraene ratios to determine essential fatty acid deficiency. No additional blood draws will be done for outpatients receiving Omegaven.

Potentially, if the subject cannot tolerate any enteral nutrition intake throughout the entire 5 month period of Omegaven, a total of 2.5 mL (less than 1 tsp) of blood may be taken.

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

N/A

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

N/A

If sample will be banked for future use:

Where will the sample be banked and for how long?

N/A

Does the banking institution have an approved policy for the distribution of samples?

N/A

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

Samples are discarded at the end of the study.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
Samples will be discarded.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
Data will not be used in the final analysis.

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
N/A

Please identify all third parties, including the subject's physician, to receive the test results.
N/A

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)
Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?
No

O1. Current Drugs

Drug : Omegaven

Is this study placebo-controlled?
No

Will the research involve a radioactive drug?
No

Section P: Device Studies

Does this research study involve the use of ANY device?
No

Section Q. Consent Form(s)

None

Section R: Advertisements

None