Study Protocol

Study Summary

Title: **Omegaven® as Alternative Parenteral Fat Nutrition**

IRB#: Pro00033519

Study Site: Tampa General Hospital

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1. Background

Parenteral Nutrition Associated Liver Disease (PNALD):

Parenteral nutrition (PN) provides intravenous (IV) 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 fat 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 PN 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 PNALD have been well described, the etiology, prevention, and treatment of this complication are not well understood. Multiple hypotheses exist to explain the pathogenesis of PNALD 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 PNALD 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 PNALD (13-15). In severe cases of refractory hepatic failure, liver transplantation with or without accompanying small bowel transplantation remains the only treatment option.

Role of IV Fat Emulsion on PNALD

Recent evidence demonstrates that lipids are metabolized differently depending on their route of administration. Enteral lipids are absorbed by the enterocyte in the small bowel mucosa in the form of a micelle and packaged into chylomicrons which are released into the portal venous system for ultimate uptake and disposal in the liver. Once in the bloodstream, these particles rapidly acquire apolipoproteins from circulating high-density lipoproteins and can subsequently be metabolized by the liver. The emulsified particles of commercially made and IV administered lipid emulsions, such as Intralipid (IL), mimic the size and structure of chylomicrons, but differ in their content. In contrast to chylomicrons, artificial lipid particles primarily contain essential fatty acids and omega-6 triglycerides and are devoid of cholesterol or protein. Recent studies suggest that these omega-6 fatty acid-containing emulsions are dependent on lipoprotein lipase, apolipoprotein E, and low-density lipoprotein receptors for clearance, and are metabolized with less lipolysis and release of essential fatty acids than are chylomicrons. In fact, it appears that they may be cleared as whole particles by tissues other than the liver. (16) These factors may account for the increased incidence of steatohepatitis associated with the IV administration of IL.

In the United States, the only FDA approved form of parenteral fat emulsions available for patients depending on parenteral nutrition (PN) is Intralipids (IL), which is composed of soybean oils, predominantly omega-6 fatty acids. In addition, Phytosterols in soybean oils are thought to have a deleterious effect on biliary secretion. Accumulation of lipids in the hepatic Kupffer cells may further impair liver function.

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).

Rationale for Omegaven® Treatment

Unlike conventional IV fat emulsions, Omegaven® is comprised solely of fish oils containing primarily omega-3 fatty acids. Animal studies have shown that IV fat emulsions such as fish oil that are high in eicosapentaenic and docosahexaenoic acid reduce impairment of bile flow as seen in cholestasis caused by conventional fat emulsions (19,20). We hypothesize that by administering Omegaven® in place of conventional phytosterol/soybean fat emulsions, that the cholestasis may be reversed and patients will be able to be maintained on adequate PN until they are able to ingest adequate nutrition enterally.

Efficacy of Treatment

Two recent studies have shown the beneficial effects omega-3 fish oil can have on the treatment of PNALD in the neonate population. A study by Gura et al (23), prospectively collected data on 18 infants with a

mean gestational age of 30 weeks, who developed PNALD and were treated with the fish-oil based lipid emulsion at a goal of 1 g/kg/day. They compared their results to a historical cohort of patients studied by Andorsky et al (22). Their primary outcome was time until reversal of cholestasis (direct bilirubin < 2 mg/dL) and secondary outcomes which included fatty acid and coagulation profiles, growth, and bloodstream infections. They found that the median time for reversal of cholestasis in the fish oil group was 9.4 weeks which was significantly less than the 44.1 weeks found the historical cohort. They also found that the fish-oil cohort had a 3.8 times greater rate of reversing cholestasis than the soybean-oil group. In terms of safety outcomes, no patients in the fish-oil cohort developed hypertriglyceridemia or coagulopathy. Also, no significant differences were seen in central venous catheter infections, new infection rates, or weight-for-age z scores.

Premkumar et al (24) enrolled 57 infants, with a median gestational age of 28 weeks, into a compassionate use protocol with the fish-oil lipid emulsion, Omegaven®. They included infants greater than 2 weeks of age but less than 6 months, a serum conjugated bilirubin > 4 mg/dL in the absence of prior gastrointestinal surgical intervention, or a serum conjugated bilirubin > 2 mg/dL with a history of gastrointestinal surgical intervention or severe feeding intolerance. The fish-oil lipid emulsion was infused at a dose of 1 g/kg/day over 24 hours. Infants were placed into 3 groups based upon the severity of their cholestasis using baseline conjugated bilirubin levels of 2, 5, and 10 mg/dL. Of the 47 survivors, all of them saw complete resolution of cholestasis independent of baseline conjugated bilirubin levels. When comparing all surviving infants, resolution of cholestasis occurred within 5 weeks of starting fish-oil emulsion. Resolution of cholestasis (conjugated bilirubin <2 mg/dL) and survival was observed in 82.5 % of infants. Of the non-survivors, causes of death were attributed to the progression of the primary disease which included multi-organ failure and sepsis. No infant developed liver failure after the start of Omegaven therapy nor were any signs of essential fatty acid deficiency seen.

Safety of Treatment

A case report looked at the long term liver function and nutritional outcomes in 2 infants who received fish oil lipid therapy (25). Each infant was started on a fish-oil lipid emulsion compassionate use protocol for intestinal failure associated liver disease. They were placed on Omegaven® for 20-25 weeks and each saw resolution of cholestasis as defined by direct bilirubin < 0.2 for two consecutive weeks. A 3 year follow-up after discontinuation of fish-oil showed continued normalization of direct bilirubin for both patients with only the patient requiring re-initiation of soybean based lipid emulsion having occasional elevated fluctuations in serum transaminases. The infant who required the restarting of their soybean based lipid emulsion saw slowed growth which may be due to inability to get the majority of caloric needs enterally. These two case reports give examples of improved liver function from initiation of fish oil without long-term adverse outcomes from long-term administration of a fish oil emulsion.

In a study by Le et al (26), 79 infants who had previously been on soybean lipid emulsion and developed PN were switched to a fish oil emulsion at a dose of 1 g/kg/day. They had a median gestational age of 91 days with a median time on the fish oil emulsion of 18 weeks. They saw significant improvements in total and direct bilirubin, serum triglycerides, total cholesterol, LDL, and VLDL. Significant decreases in omega-6 fatty acids and increases in omega – 3 fatty acids were also observed without any biochemical indication of EFA (essential fatty acid) deficiency as evident by triene:tetraene ratio below critical values. Klein et al (27) also looked at fatty acid profiles of 10 infants less than 1 year of age who were enrolled in a

compassionate use protocol of a fish oil lipid emulsion. They also observed significant increases in omega-3 fatty acids along with decreases in serum omega-6 fatty acids. Based upon triene:tetraene ratio, no biochemical indications of EFA deficiency were seen either. These two studies further reinforce the safety of a fish-oil based lipid emulsion on the fatty acid profile of infants.

2. Specific Aims and Hypotheses

To provide an alternate IV fat nutrition to help improve liver function while providing adequate nutrition for critically ill infants with parenteral nutrition (PN) associated cholestasis. Eligible infants will receive Omegaven® for compassionate use treatment purposes, for which there are no FDA approved alternative treatments.

3. Study Designs:

Omegaven® fat emulsion will be used as a Compassionate Use treatment for critically ill infants with PN associated liver injury.

After the diagnosis of PNALD is made, the patient's physician will contact an Investigator and an evaluation will be performed. If the patient's parents or guardians agree to participate in the treatment therapy, informed consent will be obtained.

Inclusion Criteria:

A. Greater than 14 days old
B. Has PN-associated cholestasis defined as at least 2 consecutive direct bilirubin >2 mg/dL with anatomical or functional short gut (OR >4 mg/dL if intact intestine) obtained at least 1 week apart with a ratio of direct: total bilirubin > 0.4
C. Patient is PN dependent (unable to meet nutritional needs soley by enteral nutrition) and are expected to require PN for at least 3 more weeks
D. Patient has not responded to other therapeutic approaches for PNALD such as : cycling of PN, avoiding overfeeding, reduction/removal of copper and manganese from PN, advancement of enteral feeding, and use of ursodiol (i.e. Actigal).
E. Patient has been on at least 2 weeks of SMOFLIPIDs with no improvement or worsening of direct bilirubin levels
F. Signed patient informed consent
G. The patient is expected to have a reasonable possibility of survival
H. No other known etiology of cholestasis other than PNALD at time of Omegaven® initiation

Exclusion Criteria:

A. Known causes of cholestasis other than PNALD including but not limited to Hepatitis C, Cystic fibrosis, biliary atresia, and alpha 1 anti-tripsin deficiency are present, prior to Omegaven® initiation
B. Known fish or egg allergy
C. Any of the contraindications to use of Omegaven®:
    a) Active new infection at the time of initiation of Omegaven®
    b) Hemodynamic instability
    c) Recent use of medications with associated risk of bleeding, including NSAIDs
    d) Active coagulopathy or bleeding
    e) Platelet counts persistently under 30,000 despite transfusions
    f) Unstable hyperglycemia

g) Impaired lipid metabolism (triglycerides >1000 mg/dL) while on 1 g/kg/day or less of Intralipid
h) History of severe hemorrhagic disorders (ie. hemophilia, Von Willebrand disease, etc.)
i) Unstable diabetes mellitus
j) Collapse and shock
k) Stroke/ Embolism
l) Cardiac infarction within the last 3 months
m) Undefined coma status

In rare instances, patients diagnosed with PNALD may later be found to have liver disease due to other causes in addition to the use of PN (i.e., inborn errors of metabolism, viral infections). These causes may not be known at the time of initiation and will not preclude this patient from continuing Omegaven®.

Baseline labs already collected as standard of care may be used provided it was collected no more than 14 days prior to the start of treatment.

Treatment Duration

A. This Compassionate Use treatment will end when the results of an FDA approved clinical trial proves Omegaven® treatment to be ineffective or the product is approved for use in the United States.
B. Patients will remain on Omegaven® until weaned from PN.
C. 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.
D. Once eligible to receive treatment, Omegaven® will be given at any time the infant requires PN and has a conjugated bilirubin > than 2 mg/dl.
E. Discontinuation of treatment would also include such factors as development of contraindications for further use or request by family / guardian to be removed from protocol.
F. In the event that a patient is unable to achieve adequate calories parenterally and is unable to tolerate enteral feeds, it may be necessary to evaluate whether or not the patient should continue the treatment with Omegaven® as monotherapy or resume therapy with conventional fat emulsions or a trial of SMOFLIPIDs for the qualified infants so that additional parenteral fat calories can be given. The attending neonatologist, in conjunction with the Principal Investigator, will determine if the patient should be removed from the Omegaven treatment protocol.

Sample Size

- The number of patients included in the Omegaven® group will be based on a compassionate use protocol and not on treatment power considerations.

4. Patient Withdrawal/ Termination

The patient will be withdrawn from the treatment after review by the Prinicipal Investigator for reasons which may include:

- Allergic reaction or anaphylaxis due to use of Omegaven®
- Active bleeding
- Hypotension during infusion
- Hyperglycemia during infusion
- Trigylcerides >600 mg/dL

- Toxicities considered unacceptable by the Principal Investigator which require adverse event assessment and reporting, are severe in nature and are related to Omegaven®. These include anaphylactic or allergic reactions,death, blood stream infections, respiratory distress, hemodynamic instability, re-hospitalization for treatment of blood stream infection, dehydration, electrolyte abnormalities, catheter malfunctions, bowel obstructions and urinary tract infection.
- Guardian requests to discontinue treatment and/or observation for any reason
- Decision by the Principal Investigator that termination is in the patient's best medical interest

In the event that the patient is withdrawn from participation, the Principal Investigator will document the date of withdrawal, the reason for withdrawal, and the results of all measurements of interest made up to date of withdrawal.

5. Omegaven Supply and Administration:

Omega-3 Fat Emulsion (Omegaven®) Supply:

Bottles containing 50mL or 100 mL of 10% Omegaven® will be purchased from Pharmacy International of Hamburg, Germany or directly from the manufacturer. Omegaven® is manufactured by Fresenius Kabi AG, Bad Homburg v.d.h, Germany. Omegaven® is formulated as an emulsion from fish oils. We are applying for FDA permission for patient insurance company billing.

All treatment materials will be stored securely until the time of administration. The bottles will be stored at room temperature below 30°C (do not freeze). Damaged or suspect drug will be returned unused to Fresenius-Kabi. Containers should be shaken before use. All supplies for the treatment will be accompanied by accountability and shipping documents and will be maintained by the Research Pharmacy at TGH. Information recorded on these accountability and shipping documents will include relevant dates, batch numbers, quantities received or dispensed, to whom dispensed, returned drug and drug lost or damaged. At the end of the treatment plan, all used and unused Omegaven® will be accounted for. If expired, the remaining drug supplies will be destroyed.

Omegaven® Administration

Therapy with Omegaven® will be initiated at the goal dose of 1 g /kg/day. The default is over 24 hours but shorter intervals may be considered if a program of TPN cycling is later recommended. Omegaven™®will be infused intravenously through either a central or peripheral catheter alone or in conjunction with parenteral nutrition. The emulsion is isotonic and is compatible with parenteral nutrition solutions and may be co-infused via y-site. Omegaven® will be infused separately from all other parenteral medications. The same standards of care provided to all patients receiving PN solution will be followed. Omegaven® will be dispensed per Tampa General Hospital policy and procedures for lipid emulsions.

Orders for Omegaven® will be written in the hospital EMR (EPIC) order form and must contain the following data elements:

- Total daily dose to administered in mL
- The hourly infusion (do not exceed maximum rate of 0.5 ml/kg/hr)
- Should not infuse without concurrent dextrose infusion

The patient will be monitored while receiving Omegaven® treatment to observe for signs of Omegaven™ toxicity. At the start of Omegaven® therapy, the patient will be monitored closely during and shortly after initial Omegaven® administration to observe for signs of allergic reaction and anaphylaxis. In the event

the patient demonstrates signs or symptoms of allergic reaction, the Omegaven® may be temporarily discontinued and the Principal Investigator and attending neonatologist will be notified. Selected safety labs will be evaluated by attending staff and the Principal Investigator.

Dose Modification / Lipid Intolerance

If lipid intolerance develops, defined as serum triglyceride levels > 300 mg/dL, the following will be considered prior to reducing the dose:

- If the level was obtained while the patient was receiving a continuous 24 hours 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.
- Other sources of lipid intolerance will be considered and addressed (drugs, renal disease)

If the triglycerides continue to remain high despite the aforementioned interventions, a dosage reduction of 25% - 50% of the current dose will be considered.

Disruption of Therapy

In event that Omegaven® cannot be administered (i.e. loss of central venous catheter access, fluid restrictions, need to administer an incompatible medication/blood product), the infusion of Omegaven® may be interrupted and resumed when the conflicting situation is resolved.

Primary Safety Outcomes/Endpoints

1. Treatment safety: Lab values will be recorded/monitored as scheduled within Table 1. Consider coagulopathy panel if suspicious for bleeding disorder. Essential Fatty Acid (EFA) Deficiency has not been reported in the use of Omegaven at 1g/kg/d. If there is clinical suspicion or prolonged use of Omegaven at <1 g/kg/d, consider testing for EFA deficiency with triene:tetraene ratio.
2. Growth: At a minimum, monitoring of growth parameters while the patient is on Omegaven® will include weight three times per week, length once weekly, and head circumference once weekly.

Table 1: Monitoring Schedule for Omegaven® Therapy

Parameter	Baseline (pre-Omegaven) No more than 14 days prior to Omegaven® treatment.	Q week*	Q 4 weeks	Periodically as clinically indicated
Weight	X			
Fluid balance	X			
Vital Signs	X			
Catheter site/function	X			
Laboratory tests:				

Hepatic Function Panel (includes Total protein, Albumin, Total and Direct Bilirubin, AST, ALT, Alkaline Phosphate)	X	X		
Renal Function Panel (includes Ca, Phosphorus, Glucose, BUN, Creatinine, Albumin, Sodium, Potassium, Chloride, CO2)	X			x
CBC without Differential (includes WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, RDW-SD)	X			x
Triglycerides	X			X
Magnesium				X
GGT	X			x

6. Monitoring for Subject/Patient Compliance

The Omegaven® will be administered by trained clinical staff and documented in the Tampa General medical records.

7. Risk/Benefit Assessment

The patient will be at some risk inherent in taking a pharmaceutical agent that has not been fully evaluated for long duration treatment. However, the availability of safety data demonstrates no life-threatening risks or toxicities to vital organs or physiologic functions. Prolonged bleeding times and inhibition of platelet aggregation are a potential risk, especially to those patients with an underlying coagulopathy or those being treated with an anticoagulant. The potential benefits of Omegaven® in this patient population are mainly based on the experimental evidence and a single case of dramatic success. However, the treatment is being used for compassionate care, as no standard therapy is available or appropriate, or has already failed. Omegaven® has been studied in animal pre-clinical models as well as Phase I, II, III, and post marketing human (adults and infants) trials.

Undesirable effects that are seen during the infusion of Omegaven® that may also occur with conventional fat emulsions (i.e., Intralipid®) include:

Uncommon: ≥ 1/1,000, <1/100:

- Slight rise in body temperature
- Heat sensation and/or cold sensation
- Chills
- Flushing or cyanosis
- Lack of appetite, nausea, vomiting
- Dyspnea
- Headache, pain in the chest, bone pain
- Priapism
- Increase/decrease blood pressure
- Anaphylactic reactions/erythema

Undesirable effects observed during the administration of Omegaven®:

Rare (≥ 1/10,000, <1/1,000):

- The infusion of Omegaven® can lead to a prolonged bleeding time and an inhibited platelet aggregation
- Fishy taste

Very rare < 1/10,000:

- Blood and lymphatic system disorders: very rare: thrombocytopenia, hemolysis, reticulocytosis
- Immune system disorders: very rare: anaphylactic reaction
- Investigations: very rare: transient increase in liver function test
- Reproductive system and breast disorders: very rare: priapism
- Skin and subcutaneous tissue disorders: very rare: rash, urticaria
- Vascular disorders: very rare: circulatory effects (e.g. hyper/hypotension).
- Thrombocytopenia has been reported in association with prolonged treatment with fat emulsions in infants. Transient increase in liver function tests after prolonged IV nutrition with or without fat emulsions have also been noted.

Other expected adverse events that are common to all patients with chronic intestinal failure, regardless of the type of fat emulsion they receive, include blood stream infections and re-admittance to hospital. Causes for re-hospitalization may include dehydration, bloodstream infections, electrolyte abnormalities, bowel obstruction, and central venous catheter malfunction.

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 >300 mg/dL acutely as a result of too rapid a rate of infusion, or chronically at high infusion rates associated with a change in the patient's clinical condition (e.g., renal dysfunction, sepsis). In such cases, the infusion will 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.

Potential Risks of No Treatment

Since Omegaven® will only be offered to those patients for whom no standard therapy is likely to be safe and effective, the risks of not being treated are those allowing for the natural history of their disease and associated clinical manifestations to progress. These include fulminate liver failure and death.

Protection Against Risks

- Treatment safety – Laboratory values will be recorded/monitored as scheduled within Table 1
- We will also monitor growth rate, weight, length, and head circumference growth

Patient Injury

In the case of injury or illness resulting from this study, emergency medical treatment is available. It will be provided at the usual charge.

Potential Benefits to the Patients

- 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.

- The potential benefits of this therapy apply directly to the patient in question and to possible improvement in the treatment of future patients. If successful, the experimental treatment will provide a safe and effective means of avoiding liver failure requiring transplant or that may lead to death. Thus, the potential complications of surgery or fulminant hepatic failure may be avoided.
- PN associated liver disease is a life threatening condition. Available therapies (liver/small bowel transplant, intestinal lengthening, ursodiol, combination enteral/parenteral feedings) are often inadequate. Phytosterol containing IV fat emulsions containing large quantities of omega 6 fatty acids have been associated with PN associated liver disease. The safety profile of Omegaven® has been demonstrated to be acceptable for the diseases treated and should be considered as an option for patients requiring a form of IV fat emulsion.

Alternatives to Participation

The only other alternative is the FDA approved soybean emulsion. Non-FDA approved fat emulsion, SMOFLipids, is also available at TGH for certain population.

8. Unanticipated Problems

Adverse events (AEs) will be assessed and reported from the time of the first Omegaven® infusion until exit from the treatment plan in accordance with USF IRB and FDA reporting requirements. If the patient experiences any adverse events that are moderate or severe in nature and that may be related to Omegaven® will have their treatment temporarily halted until the adverse event has resolved. Dose modifications will occur as described above. If a dose reduction is made for adverse events later considered to be unrelated to Omegaven®, the Omegaven® dose will be increased back to the dose prescribed prior to the dose reduction. If the patient has an anaphylactic or allergic reactions will not continue Omegaven® treatment.

Adverse events will be detected by TGH NICU medical and nursing staff during provision of standard care services including the routine monitoring of vital signs and daily physical exam data. Adverse events identified by staff will be reported to the Principal Investigator and research team per USF IRB policy.

9. Data Collection for Quality Improvement: Beside monitoring for undesirable effects and safety, we will also collecting data, such as growth paremeters, peak serum direct bilirubin, length of PNALD, length of stay, time to full enteral feeds, ect…, to compare the the impact on clinical outcomes before and after the implimentation of this Omegaven protocol.

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