Official Title: Use of a Fish Oil-Based Intravenous Lipid Emulsion (Omegaven®) in the Treatment of Parenteral Nutrition (PN) Induced Liver Injury
NCT01845116
Date: 7/21/2010

CAROLINAS HEALTHCARE SYSTEM
EXPERIMENTAL DESIGN/STUDY PROTOCOL
July 21, 2010

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Use of a Fish Oil-Based Intravenous Lipid Emulsion (Omegaven®) in the Treatment of Parenteral Nutrition (PN) induced Liver Injury

BRIEF SUMMARY OR ABSTRACT OF THIS PHASE II CLINICAL TRIAL STUDY PROTOCOL

In the United States, patients dependent upon parenteral nutrition (PN) receive parenteral lipid emulsions composed of soybean oils. Lipids are necessary in PN dependent patients due to their high caloric value and essential fatty acid content. They have been implicated in predisposing patients to PN associated liver disease (PNALD). Phytosterols such as those contained 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.

Children requiring prolonged courses of PN are at risk for developing PNALD. It is s hypothesized that although omega-6 fatty acid emulsions prevent fatty acid deficiency, they are not cleared in a manner similar to enteral chylomicrons and therefore accumulate in the liver and result in steatotic liver injury. It is further hypothesized that a fat emulsion comprised of omega-3 fatty acids (i.e., fish oil) such as Omegaven® would be beneficial in the managemet of steatotic liver injury by its inhibition of de novo lipogenesis, the reduction of arachidonic acid-derived inflammatory mediators, prevention of essential fatty acid deficiency through the presence of small amounts of arachidonic acid, and improved clearance of lipids from the serum. Animal studies have shown that IV fat emulsions (IFE) such as fish oil that are high in eicosapentaenic and docashexaaenoic acid reduce impairment of bile flow which is seen in cholestasis caused by conventional fat emulsions. Furthermore, it is hypothesized that intravenous omega three fatty acids will be well tolerated and might reduce the inflammatory effect in the liver of prolonged PN exposure and could potentially reverse any hepatic dysfunction due to PN/IFE use. By administering Omegaven® in place of conventional phytosterol/soybean lipid emulsions, we may reverse or prevent the progression of PN associated cholestasis and thus allow the patient to be maintained on adequate PN until they are able to ingest adequate nutrition enterally.

PHASE II CLINICAL TRIAL HYPOTHESIS

The administration of Omegaven® in place of conventional phytosterol/soybean lipid emulsions will be safely provided to children with intestinal failure (defined as inability to wean from PN, with causes including short bowel syndrome) and PNALD and will reverse or prevent the progression of PN associated cholestasis and will allow the patient to be maintained on adequate PN until they are able to ingest adequate nutrition enterally.

SPECIFIC AIMS/OBJECTIVES

- To determine the impact of Omegaven® on reversal of conjugated hyperbilirubinemia
- To determine the impact of Omegaven® on the prevention of essential fatty acid deficiency
- To determine the impact of Omegaven® administration on serum triglyceride
- To determine the impact of Omegaven® administration on coagulation profiles

BACKGROUND AND SIGNIFICANCE

Parenteral Nutrition Associated Liver Disease (PNALD)

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 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, are 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, systemic infections, 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 liver disease 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.

Role of Intravenous Fat Emulsion on PN Associated Liver Disease

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 intravenously administered lipid emulsions, such as Intralipid®, 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 intravenous administration of Intralipid®.

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).

Table 1 summarizes the composition of Intralipid® and Omegaven fat emulsions.

Rationale for Omegaven® Treatment

Unlike conventional intravenous fat emulsions, Omegaven® is comprised solely of fish oils containing primarily omega-3 fatty acids. Animal studies have shown that IV lipid 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). By administering Omegaven® in place of conventional phytosterol/soybean fat emulsions, 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.

PRELIMANARY STUDIES/PROGRESS REPORT

Animal Studies

The development of PN-associated liver injury may be dependent on both the route and quantity of lipid administration. Also, omega-3 fatty acids are thought to prevent or reduce de novo lipogenesis and the subsequent liver injury independent of the route of administration. Specifically, a previously established murine model of PN-associated liver injury was used to investigate whether enteral lipid administration would protect against the development of steatohepatitis in PN-dependent animals. In this murine model, steatohepatitis is largely due to a high carbohydrate load and essential fatty acid deficiency. Although this model is not replicative of the clinical setting, it is a model that maximizes liver steatosis. In this model, mice are treated with oral PN for 19 days before being sacrificed. These animals develop severe fatty liver changes demonstrated by MRI spectroscopy and histology (H&E, PAS, and oil red O staining), and also have biochemical changes consistent with liver injury (elevated alkaline phosphatase and serum transaminases). Experimental groups were supplemented with Intralipid® by several routes of administration including orally, intravenously, and subcutaneously. Other groups were also supplemented with omega-3 fatty acids (Omegaven®) by the same routes of administration. This study found a consistent pattern of protection against PN-associated steatohepatitis by administering enteral Intralipid® (22). In mice that received the highest dose of enteral Intralipid®, there was a marked decrease in the extent of overall liver injury as measured by gross inspection, histologic analysis, liver fat content, and serum liver enzyme levels. In all areas of this investigation, mice treated with enteral lipid most closely resembled the control mice that did not receive PN as part of the experimental protocol. These results were in complete contrast to the extensive fatty infiltration and evidence of hepatic injury found in mice that received PN without lipid supplementation, as well as in mice that received PN with intravenous Intralipid®. Mice receiving intravenous Intralipid® had the most severe liver changes. Both groups of animals developed marked hepatic steatosis with macrovesicular fatty infiltration and significant elevations in spectroscopic liver fat content and serum transaminase levels. In addition, the effect of enteral Intralipid® supplementation appeared to be dose-dependent; mice receiving one-third the dose of enteral Intralipid® showed improved liver histology but still demonstrated a moderate degree of liver injury by spectroscopy and serum liver function tests.

The nutritional model employed in this study provided all experimental mice with enteral PN solution ad libitum. In this way, mice were not force-fed PN and self-regulated their PN intake by demands for growth and energy. Importantly, all mice gained weight throughout the 19-day protocol, and there were no differences in weight gain parameters between the groups. The PN solution was a typical pediatric stock containing 20% dextrose and 2% amino acids. Each milliliter of this formula provides 0.2 g (0.68 kilocalories) of dextrose and 0.02 g (0.08 kilocalories) amino acid. As the daily intake per animal of PN averaged 15 ml, mice were ingesting approximately 11.4 kilocalories/day and 456 kilocalories/kg/day. This caloric load is similar to the established dietary energy needs of the mouse (23). The parenteral fat source used in this study was Intralipid® 20% (Baxter, Deerfield, Illinois), which is a soybean oil-based emulsion. Each milliliter of this emulsion contains 0.2 g (2.0 kcal) of fat. It is recognized that the model may not completely match the clinical, human setting of intravenous PN-administration; however, the goal was to produce a fatty liver with biochemical evidence of injury.

In a second set of experiments, the same murine model was used to determine whether Omegaven®, a commercial fish oil emulsion available in Europe, would prevent fatty liver changes by enteral or parenteral routes of administration, and to determine the serum fatty acid profile of these animals. Animals receiving Omegaven® via the oral and intravenous routes had completely normal livers on histology and MRI spectroscopy revealed normal liver fat content. Liver functions tests in orally treated animals were also within the norm, while there were minimal elevations in intravenously treated groups. There was no fatty acid deficiency in these groups as determined by Mead acid (5, 8, 11-Eicosatrienoic acid) levels in the serum fatty acid analysis. Mead acid is the only polyunsaturated fatty acid of note produced de novo by animals and only accumulates under the conditions of essential fatty acid deficiency. Furthermore, arachadonic acid levels were low in Omegaven® treated animals consistent with previous reports. In a third set of experiments, mice were made severely fatty acid deficient. These mice were treated for 10 days with Omegaven® and had complete reversal of their fatty acid deficiency.

Similarly, other investigators studied livers in a newborn pig model and showed that intravenous administration of fish oil, which consists primarily of omega-3 fatty acids, reduced parenteral nutrition-induced cholestasis.(22) However, the study was only 3 weeks in duration and long-term effects from administration of omega-3 fatty acids alone were not evaluated. In fact, the idea that one could remove an essential fatty acid from the standard regime of nutritional support by PN has not been accepted. It has been thought that reduction of an essential fatty acid, such as omega-6, during long-term therapy would result in fatty acid deficiency and deterioration of the health of the patient. The Children's Hospital Boston's experience to date, demonstrates that the use of Omegaven® as monotherapy does not result in the development of essential fatty acid deficiency and it can actually be used to as monotherapy to treat this deficiency state.

Preliminary Safety and Efficacy Data for Use of Omegaven® in Other Diseases

Omegaven® has been used for over 10 years as an adjunct to conventional fat emulsions. According to current data, an increase in the proportion of omega-3 fatty acids is thought to optimize nutrition in general, but in particular benefit patients whose underlying disease might benefit from an increase in omega-3 fatty acids. An adequate intake of omega-3 fatty acids results in anti-inflammatory and immunomodulatory effects that are protective in nature from inflammatory tissue damage, capillary permeability, and improved immunological resistance. It may also reduce the risk of thrombosis and increase microvascular perfusion due to its anti-aggregatory and vasodilatory effects.

In Europe and Asia, the use of parenteral omega-3 fatty acids has been used in the following adult patient populations (24-28):

- Post traumatic and post surgical patients
- Patients experiencing early stages of sepsis/SIRS
- Patients at risk of hyperinflammatory processes
- Patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis)

- Patients with inflammatory skin diseases (psoriasis, atopic eczema)

The dosing used in these patients was 0.1 g (1 ml) to a maximum of 0.2 (2 ml) /kg body weight. The infusion rate used did not exceed 0.5 ml/kg/body weight/hour. Since it was intended to be infused in combination with conventional fat emulsions, the total fat intake was limited to 10-20% as fish oil. The duration of administration did not exceed 4 weeks.

Preliminary Safety and Efficacy Data for Use of Omegaven® in Infants

Initial pediatric experience with Omegaven® was limited to 2 unpublished clinical trials (see reference). These trials were performed in Germany and Taiwan (29). The German study was a controlled, randomized, open parallel-group clinical study to investigate whether or not omega-3 fatty acids could be incorporated into the plasma phospholipids of very low birth weight preterm infants. In this 7-day safety trial, Omegaven® use was evaluated on the basis of clinical, laboratory, and antioxidant parameters and lipid metabolism. Treatment was started on day 3-5 of life and continued for a total of 7 days. Patients received Omegaven® plus conventional soybean fat emulsion or soybean emulsion alone. The maximum dose of Omegaven® in the study was 0.2 gm/kg/day. The study concluded that the Omegaven® was well tolerated in this group of preterm infants in respect to both hematological and biochemical parameters. The incidence of reported adverse events between both study groups was similar. The eicosapentaenoic acid (EPA) content of plasma phospholipids increased significantly in the Omegaven® arm, with the proportion of EPA to the total fatty acids reaching almost three times the baseline value. The sum of omega-3 fatty acids showed a significantly greater increase in the Omegaven® group compared to the conventional treatment arm.

The Taiwanese study was a single center, controlled, open-labeled study conducted to investigate the safety of parenteral administration of Omegaven in preterm infants. The group of 20 infants were randomized to one of two treatment groups; one consisting of Omegaven®/conventional lipids and the other consisting of conventional lipids alone. The average dose of Omegaven® in the treatment group of this 14-day study was 0.13 + 0.02 g/kg/day. There were no significant differences between the two groups with regard to body weight and length. Similarly, there was no significant difference in the hematological or biochemical parameters. There were no adverse events that were attributable to Omegaven® use. It was concluded that Omegaven® was well tolerated in these preterm infants.

Experience in PN Liver Injury

A single patient with bridging fibrosis due to prolonged parenteral nutrition use has been treated by compassionate use with Omegaven® at Children's Hospital, Boston (IRB approval # E04-09-006, FDA IND # 69,208). By age 6 months, this male infant was listed for a liver-small bowel transplant due to severe hepatic disease. His liver biopsy showed predominantly centrilobular, hepatocellular damage with ballooning of the hepatocytes, cholestasis, local steatosis, focal giant cell transformation, expansion of

portal tracks with mild inflammation, bile duct proliferation, mild fibrosis, and mild periportal iron deposits. On a subsequent biopsy, he progressed to bridging fibrosis. Omegaven® was started at a dose of 0.2 g/kg/day IV and advanced by 0.2 g/kg/day increments to 1 g/kg/day over a 14-day period. In order to ensure adequate caloric intake, additional non-protein calories were provided as parenteral carbohydrates (as dextrose). No other parenteral form of fat emulsion was administered during Omegaven® therapy. His enteral feeds were advanced while on the Omegaven®. Once the goal dose of Omegaven® was reached, the direct bilirubin declined and normalized. His AST also normalized and he was removed from the liver-small bowel transplant list. Weekly CRP levels were obtained to monitor systemic inflammation. CRP levels decreased from a high of 1.85 to 0.17 mg/dL (Normal <0.5). He continues to receive Omegaven® at a dose 1g/kg/day and has had no evidence of bleeding or clinical evidence of essential fatty acid deficiency. His direct bilirubin continues to be within the normal range and he has no evidence of jaundice. He is still receiving approximately 50% of his total caloric needs via the parenteral route. He continues to grow and is achieving his developmental milestones appropriately. This child has been on Omegaven® for greater than 5 years.

Since the time of this initial patient, an additional 130 patients have been treated with Omegaven® at Children's Hospital of Boston. In addition to the aforementioned patient, 24 children are receiving Omegaven® at home in conjunction with home parenteral nutrition. As of January 6, 2006, no patients from Children's Hospital of Boston receiving Omegaven® have died of PN associated liver disease or required a liver transplant.

In a recent article by Lee et al, entitled "*Impact of fish oil-based lipid emulsion on serum triglyceride, bilirubin, and albumin levels in children with parenteral nutrition-associated liver disease*", published in Pediatric Research (December, 2009), the authors demonstrated that substituting fish oil-based lipid emulsion for the standard soybean-based emulsion will result in normalizing, to some degree, the altered physiologic balance that comes to exist in patients dependent on PN. The indices that have shown improvement were decreasing direct bilirubin and triglyceride levels and increasing albumin levels. In previous publications, these authors have also noted that the provision of fish-oil-based fat emulsion was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, infections, or growth delay.

Researchers at The Hospital for Sick Children, Toronto, Canada published their findings of their experience with Omegaven® in young children in a recent publication (February, 2009) The median age was 7.5 (range 3.6-46) months, and median parenteral nutrition duration before starting Omegaven® was 28.4 (range 15.3-55.3) weeks. Median initial serum conjugated bilirubin was 137 (range 54-203) micromole/L (8.06 [3.18-11.94] mg/dL). Nine of the twelve patients had complete and sustained resolution of hyperbilirubinemia within a median of 24 (range 7-37) weeks, and all were no longer being considered for liver transplantation. Improvements in markers of hepatic inflammation as well as nutritional status also were noted in these patients. Three of the 12 patients received a liver-intestine transplant while taking Omegaven®. There were no complications attributable to Omegaven®.

DESIGN AND METHODS

Study Design

This phase II clinical trial will be a non-randomized, open-labeled, prospective study of intravenously administered Omegaven® fat emulsion in the treatment of PN associated liver injury.

Patient Selection and Inclusion/Exclusion Criteria

After the diagnosis of PN liver injury is made, patients who are followed by the Neonatology, Gastroenterology, Surgery, or the Critical Care Service in conjunction with the patient's primary physician will contact Drs. Caicedo, Chiu, or Lessaris, and an evaluation will be performed. If the patient's parents or guardians agree to participate in the study, informed consent will be obtained. The history of present illness and past medical history will be reviewed with the guardian and pertinent demographic and medical information will be recorded on data collection forms. These forms will be used to record all laboratory results, nutritional history, and descriptions of any liver biopsies performed.

Though most patients receiving parenteral nutrition do not develop end stage liver disease, there is a small percentage of patients, typically infants and children on prolonged courses of parenteral nutrition, who do go on to develop fulminant liver failure. The study population of this protocol is limited to patients felt to fulfill the following conditions:

a) The patient will be PN-dependent (unable to meet nutritional needs solely by enteral nutrition) **and**
b) The patient will have significant hepatic dysfunction due to PN despite utilization of all conventional therapies (the patient must have failed standard therapies to prevent the progression of his/her liver disease including surgical treatment, cycling of PN, reduction/removal of copper and manganese from PN, advancement of enteral feeding, and the use of ursodiol).

Inclusion Criteria:

1. Children 0-18 years of age
2. Patients will be PN-dependent and expected to continue PN for at least 30 days
3. Patients considered eligible for study participation must have PN-associated liver diseases . Other causes of liver disease (i.e., biliary atresia, galactosemia, alpha-1 antitrypsin deficiency) will be excluded. A liver biopsy is not necessary for treatment
4. Direct bilirubin > 2.0 mg/dl
5. Signed patient informed consent
6. Signed patient assent where applicable.

The patient will be hospitalized at the time of enrollment and initiation of Omegaven®.

Exclusion Criteria:

1. Pregnancy
2. Other causes of chronic liver disease (cystic fibrosis, biliary atresia, alpha-1 antitrypsin deficiency)
3. Signs of advanced liver disease including cirrhosis on biopsy, varices, ascites
4. The patient is allergic to eggs/shellfish
5. The patient has a severe hemorrhagic disorder
6. The patient is enrolled in any other clinical trial involving an investigational agent (unless approved by the designated physicians on the multidisciplinary team)
7. The parent or guardian or child unwilling to provide consent or assent.

Screening Procedures

Prior historical and physical information, imaging studies, biopsies, and other available specialized tests will be reviewed by the multidisciplinary team experienced in the diagnosis and treatment of parenteral nutrition associated liver disease. Additional biochemical monitoring will be perfomed as necessary. If the patient's status supports consideration of treatment, the option for non-experimental therapy will be investigated.

Recruitment Methods

With an anticipated enrollment of 3-5 patients per year, 20-25 patients will be recruited over the course of the 5 year study.
Patients in the trial will be recruited from the NICU, PICU, CVICU, surgery, gastroenterology, and general pediatrics services at Levine Children's Hospital (LCH). Approximately 5-8 patients/year are diagnosed with severe PN associated liver injury at Levine Children's Hospital. The Principal Investigator (Dr. Caicedo) or Co-investigators (Dr. Chiu, Dr. Lessaris) will discuss treatment options including study treatment with the parents or legal guardians. Informed consent for participation in the study will only be obtained by physicians who are able to fully inform the patients of alternatives to participation. If the patient is a minor but of sufficient age and understanding, patient assent will also be obtained.

Description of Study Treatments or Exposures/Predictors

Bottles containing 50mL or 100 mL of 10% Omegaven® will be purchased from International Pharmacy of Hamburg, Germany. Insurance companies will be billed the cost of Omegaven®. If the insurance company does not provide payment, *Healthy @ Home, LLC* will cover all drug costs for patients enrolled in this protocol. Omegaven® is manufactured by Fresenius Kabi AG, Bad Homburg, Germany. Omegaven® is formulated as an emulsion from fish oils.

While inpatient, the emulsion for each patient will be provided in its original container for volumes more than 96 ml/day. Doses less than 96 ml/day will be repacked into syringes to allow for administration via syringe pump. If patients are to be discharged home on Omegaven®, all doses will be administered from the original manufacturer's container.

Outpatients will have laboratory data monitored (Table 2) as do inpatients, with values reported to the pediatric gastroenterologists via the Pediatric Nutrition Support Clinic at the Levine Children's Specialty Center. Growth will be tracked weekly. Home health nursing staff and guardians will be educated regarding Omegaven® and administration while the child is still an inpatient prior to discharge. This education will include Omegaven® adverse event monitoring (Table 3) and reporting; administration practices; and information regarding monthly or other mutually agreed upon schedules for clinical evaluation and follow up of the patient by study investigators.

All study 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 study protocol will be accompanied by accountability and shipping documents and will be maintained by the Investigator or deputy (e.g. research pharmacist). 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 protocol study, all used and unused Omegaven® will be accounted for. If expired, the remaining drug supplies will be destroyed.

Financial Consideration
A request to charge for Omegaven® has been submitted to the FDA. *Healthy @ Home, LLC* will assume all costs, in the event that third party payers do not cover the cost of Omegaven®. Study investigators will not receive financial benefit in any form from this research study.

Details of Omegaven® Administration
After baseline labs are obtained (Table II), therapy with Omegaven® will be initiated at a starting dose of 0.5gm/kg/day infused over 12-24 hours. After two days, the dose will be increased to 1 gm/kg/day, the goal dose. Omegaven® will be infused intravenously through either a central or peripheral catheter in conjunction with parenteral nutrition. The same standards of care provided to all patients receiving parenteral nutrition solution will be followed. Laboratory tests will be performed as detailed in Table 2. Growth will be tracked weekly. If additional fat calories are needed, they will be provided via the enteral route.

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 study with Omegaven® as monotherapy or resume therapy with conventional fat emulsions at 1 gm/kg in addition to the Omegaven® so that additional parenteral fat calories can be given. The clinical team, in conjunction with the patient's primary physician, will determine if the patient should be removed from the protocol.

As previously mentioned, Omegaven® may be infused in the same manner as conventional fat emulsions through either a central or peripheral line. The emulsion is isotonic. It is compatible with parenteral nutrition solutions and may be co-infused via y-site. Omegaven® may be infused through a 1.2micron inline filter.

Dose Modification
Hypertriglyceridemia:
If hypertriglyceridemia develops, defined as serum triglyceride levels > 200 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.

Hyperglycemia:
If hyperglycemia develops, defined as serum glucose levels >250mg/dL, other sources of hyperglycemia should be considered and addressed (sepsis). A minimum dosage reduction of 25% will occur. Blood sugars will continue to be monitored closely with additional adjustments as warranted.

Coagulopathy:
Other sources of coagulopathy should be considered and addressed (sepsis, worsening liver failure). Omegaven administration will be reduced or halted. Coagulation profiles will continue to be monitored closely with additional adjustments as warranted.

Duration of Therapy
Patients will complete the study when he/she is completely off PN; develops a contraindication for further use; or the patient/family requests to be removed from the study protocol.

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.

In the event that a patient whose hepatic enzymes and serum bilirubin have normalized still requires parenteral fat emulsion after receiving Omegaven® for more than 6 months, their clinical course will be reviewed, and a decision will be made whether to continue the Omegaven® or rechallenge the patient with conventional therapy (Intralipid®).

Discontinuation of Therapy
Patients will continue to be followed by the Nutritional Support Program (LCH Division of Gastroenterology) upon discontinuation of therapy with Omegaven® a minimum of 3 months after the treatment is stopped. In addition, patients will be contacted annually for 5 years following completion of the study, to ascertain growth, well being and PN dependency.

Resumption of Therapy
In the event that a patient who has been off the protocol more than 3 months must receive intravenous fat emulsion, treatment with Omegaven® will resume only if the patient shows evidence of PN liver disease (elevations in direct bilirubin > 2 or pathology findings consistent with cholestasis). Otherwise, the patient will be treated with conventional lipid emulsion.

Definition of Primary and Secondary Outcomes/Endpoints
The primary outcome is normalization of direct bilirubin to less than 0.4mg/dL by 9 months.
Seconday outcomes include:

- Omegaven® will prevent EFA deficiency as evidenced by normal EFA profiles on monthly evaluations
- The rate of triglyceride levels > 400 mg/dL with Omegaven® will be similar to that seen with PN administered with soy oil IFE (conventional emulsion, i.e., Intralipid®) as evidenced by baseline data and then weekly and monthly evaluations
- PN containing Omegaven® will be safe for patients with respect to the risk of unexpected bleeding/coagulopathies as evidenced by weekly and monthly evaluations

Data Collection Methods/Assessment and Schedules
Data will be collected by the PI and the co-investigators. Hospital charts will be reviewed for pertinent clinical information. Results of liver biopsies and blood chemistries will be obtained from the Cerner Power Chart computer system. Specifically, the history of present illness, past medical history, and birth history, pertinent physical exam findings including patient weight, the results of liver biopsies, and parenteral and enteral feeding history will be collected. The information will be recorded on hard copy data collection forms.

Study Protocol Timeline
This study protocol will end five years following commencement of the study.

Adverse Event Criteria and Reporting Procedures
Adverse events (AEs) will be assessed from the time of the first Omegaven® infusion until exit from the study. In particular, the patient will be observed during and shortly

after Omegaven® administration for the occurrence of anaphylactic or allergic reactions. Patients experiencing 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 in the event of hypertriglyceridemia, hyperglycemia and coagulopathy will occur as described above. Should patients be dose reduced for adverse events that are later considered to be unrelated to the study medication, treatment will recommence at the dose they had received prior to the dose reduction. Patients with anaphylactic or allergic reactions will not continue Omegaven® treatment.

Any serious or unsuspected adverse events will be reported to the Institutional Review Board and to the FDA within 72 hours of the occurrence, or immediately if the event is fatal or life threatening as per CHS IRB Policy on Adverse and Unexpected Events and Unanticipated Risks to Research Subjects and Others. This will be done in person or by telephone, and by completion of the IRB form for adverse/unexpected event reporting.

Unanticipated adverse events will be detected by the monitoring of vital signs, physical exams and laboratory analysis for all participants, as well as by observation by the nursing staff and guardians (following instruction) if participant is an outpatient. Events will be reported to the investigators immediately by telephone or pager, and subsequently to the appropriate board or committee.

The IRB will be responsible for assuring that adverse event reporting requirements are met. Any patients who have agreed to participate in the study protocol, but who have not yet undergone intervention, will be informed of the adverse event.

All AEs will be assessed by the Investigator and recorded in a case report form, inclusive of the date of onset and resolution; severity; relationship to study medication; outcome and action taken with the study medication. In addition, the clinical severity of all AEs will be recorded and graded using the standard definitions of mild, moderate, severe or potentially life threatening with serious adverse events (SAE) deemed to be those severe to potentially life threatening (Table 3). Once an AE or SAE is identified, research team members will ensure that the participants receive appropriate care and that all actions taken by the PI after observing the AE or SAE are documented. In addition, all AE or SAEs will be classified and documented by the Investigator as definitely, probably, possibly, or probably unrelated to administration of study drug.

Patients will be withdrawn from the study for any of the following:

a) Toxicity considered unacceptable by the Investigator
   note: no adverse effects have been observed in patients receiving Omegaven® that could be attributed to its use
b) Patient/guardian requests to discontinue treatment and/or observation for any reason
c) A suitable organ has been located and the patient is able to undergo a liver or liver/intestinal transplant
d) Decision by the Investigator that termination is in the patient's best medical interest

e) Patient is lost to follow-up.

In the event that a patient is withdrawn, the Investigator will document the date of withdrawal, the reason for withdrawal, and the results of all assessments made up to the date of withdrawal.

DATA MANAGEMENT AND STATISTICAL ANALYLSIS

Data Management Methods

Overview

This phase II clinical trial study will be supported by an Access-based data management system (DMS). The system will include a protocol management system that assists study staff with accurate collection of study data and monitors protocol adherence. The system will provide and be linked to a data entry system. Features of the system include double data entry, data range and logic checks, cross form validations at the time of data entry and audit trails of entered and corrected data.

Protocol Management and Protocol Status

All study related tasks will follow Good Clinical Practice Guidelines. Protocol status reports from the protocol management system will allow the principal investigator to monitor protocol adherence on a regular basis.

Data Entry and Databases

Study results will be entered into the DMS from paper based case report forms that will be completed by the investigators.

Confidentiality, Security, Back-Up

The databases will be located on the CHS Network and therefore backed - up on a daily basis. All study files will be password protected to ensure patient confidentiality and security of the database.

Quality Control Methods

Dispensing of Study Drug

Pharmacy dispensing records will be reviewed by a study monitor on a monthly basis to ensure adherence with procedures for dispensing of Omegaven.

Legal and Ethics Requirements

This study is being conducted under a FDA Investigational New Drug Application. FDA guidelines must be followed. Federal regulations require all investigational studies be conducted under the auspices of an IRB, as defined in the Code of Federal Regulations,

Title 21, Part 56; and in accordance with the Declaration of Helsinki (1964) amended Edinburgh, Scotland (2000). The IRB will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent prior to the initiation of the study. All changes to the protocol or consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

Informed Consent

The Investigator 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 original of the signed consent must be maintained in the patient's medical record. The person who signed the consent must also be given a copy of the signed consent form.

Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those cited below, is prohibited. Patient confidentiality will be further ensured by utilizing patient identification code numbers and patient initials. Data generated as a result of this study will be available for inspection, on request by various regulatory agencies. These shall include all study-relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the patient is on study, and autopsy reports (if available) for deaths occurring during or in temporal proximity to the study.

As part of the required content of the informed consent, patients must be informed that their records will be reviewed by various regulatory agencies.

Retention of Records

The Principal Investigator and study staff will maintain a comprehensive and centralized filing system of all study related documentation which is suitable for inspection at any time by various regulatory agencies. These include:

a. Patient files including source documentation and Informed Consent
b. Study files, including the protocol with all amendments, copies of all regulatory documentation, and all correspondence with the FDA and IRB
c. Pharmacy files including drug shipment, dispensing, and accountability records, and pharmacy-related correspondence

Per FDA regulations, the Primary Investigator will retain records for a period of two (2) years following discontinuation of the study.

Data Analysis Plan

The study protocol is intended to evaluate the safety and efficacy of Omegaven® in the treatment of PN induced liver injury. Safety is addressed in the Data and Safety Monitoring Plan. Serum markers for efficacy will be monitored (bilirubin and liver enzymes). The specific data analysis will be evaluated by our statistician.

Statistical Power and Sample Considerations

As discussed above, this study protocol is not intended to prove statistical significance.

Study Organization

Dr. Caicedo will serve as the principal investigator. The investigators will perform all data collection and data entry. Drs. Chiu and Lessaris will assist with patient enrollment. Drs. Caicedo, Chiu and Lessaris will assist in study design and data analysis.

Data and Safety Monitoring Plan

Monitoring for toxicity due to Omegaven will be assessed by analyzing clinical and laboratory parameters including serum electrolytes, hematological studies, serum triglycerides, total cholesterol, essential fatty acid profiles, blood and urine glucose and liver and renal function tests. Blood samples will be taken prior to the start of therapy, and weekly thereafter until direct bilirubin <2mg/dL. Subsequent testing will be determined based on direct bilirubin values (as this is the monitoring standard of care for liver failure) and will be bimonthly or monthly. See Table 2 for additional information. Dose reduction will occur if there is evidence of hypertriglyceridemia (serum triglycerides > 200mg/dL), hyperglycemia (serum glucose >250mg/dL), or evidence of bleeding. Growth indices including weight, length/height, and head circumference will also be monitored. Dr. Pineiro, the director of Pediatric Gastroenterology at LCH will be the Data and Safety Monitor. He will review patient data quarterly to ensure patient safety is upheld and that protocols are followed as described. The study will be halted in the event of one life threatening episode related to Omegaven® administration.

RSKS AND DISCOMFORTS

Description of Risks and Discomforts

Potential Risk of Omegaven® Treatment

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 hemorrhagic disorders
Unstable diabetes mellitus
Collapse and shock
Stroke/ Embolism
Recent cardiac infarction
Undefined coma status
Known allergy to fish or egg protein

Side effects:

The infusion of Omegaven® can lead to a prolonged bleeding time and an inhibited platelet aggregation. In rare cases, patients may experience a fishy taste.

The administration of Omegaven® should be stopped or reduced if there is a marked increased in blood glucose levels during the Omegaven® infusion. Undesirable effects that are seen during the infusion of Omegaven® that may also occur with conventional fat emulsions (i.e., Intralipid®) include:

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

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 >200 mg/dL 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.

Potential Benefit of Omegaven® Treatment

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.

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 fulminant liver failure and death.

Summary – Overall Risk Assessment

Patients 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; a highlighted case of dramatic success; and success in phase I clinical trials. However, the study will only be available to those for whom no standard therapy is available or appropriate, or has already failed. The risks and potential benefits will require careful individual assessment by both the investigators and patients. The heterogeneity of clinical manifestations will lead to non-uniform risk-benefit ratios across the eligible patient population.

Privacy Provisions

Individual patient medical information obtained as a result of this study protocol is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Patient confidentiality will be further ensured by utilizing initials. Data generated as a result of this study will be available for inspection, on request by various regulatory agencies. These shall include all study-relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the patient is on study, and autopsy reports (if available) for deaths occurring during or in temporal proximity to the study.

Confidentiality Provisions

Loss of patient confidentiality is another risk in this study. The risk of loss of confidentiality will be reduced by the study database being password protected and the use of initials as patient identifiers.

POTENTIAL BENEFITS

The potential benefits of this study protocol apply directly to those seen in phase I clinical trials 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 potenital 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 or entail high risks. Phytosterol-based intravenous fat emulsions containing large quantities of omega 6 fatty acids have been associated with PN associated liver disease. For example, one patient, with bridging fibrosis secondary to prolonged PN/lipid therapy, treated with Omegaven® has had a sustained dramatic response with resolution of jaundice and direct bilirubin levels < 2. 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 intravenous fat emulsion.

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Table 1

Comparison of Parenteral Fat Emulsions (10 grams fat/100 mL)

OIL	Intralipid®	Liposyn® II	Omegaven®
Soybean	10	5	
Safflower		5	
Fish			10
% FATS			
Linoleic	50	65	0.1-0.7
α-linolenic	9	4	<0.2
E.P.A.			1.3-2.8
D.H.A.			1.4-3.1
Arachidonic acid			0.1 -0.4
Glycerol	2.3	2.5	2.5
Egg Phospholipid	1.2	1.2	1.2
Available in the United States	Yes	Yes	No

Table 3:

Laboratory Monitoring Schedule for Omegaven® Therapy

Laboratory test:	Baseline (pre-Omega-ven®)	Q week* Until Direct Bilirubin < 2mg/dL	Bimonthly * Until Direct Bilirubin <0.4 mg/dL	Monthly* once direct bilirubin <0.4 mg/dL
Sodium	X	X	X	X
Potassium	X	X	X	X
Chloride	X	X	X	X
Glucose	X	X	X	X
BUN	X	X	X	X
Creatinine	X	X	X	X
Triglycerides	X	X	X	X
Calcium	X	X	X	X
Magnesium	X	X	X	X
Phosphorus	X	X	X	X
Prealbumin	X	X	X	X
Albumin	X	X	X	X
Total protein	X	X	X	X
SGPT	X	X	X	X
Alkaline phosphatase	X	X	X	X
Bilirubin (total & direct)	X	X	X	X
GGT	X	X	X	X
AST	X	X	X	X
Essential Fatty Acid Profile	X	X	X	X
Free cholesterol	X	X	X	X
Free fatty acids	X	X	X	X
Lipid Panel	X	X	X	X
Hemoglobin	X	X	X	X
Hematocrit	X	X	X	X
RBC	X	X	X	X
WBC	X	X	X	X
Platelets	X	X	X	X
PT	X	X	X	X
PTT	X	X	X	X
INR	X	X	X	X
Fibrinogen	X	X	X	X

* Direct bilirubin evaluations guide further testing as this value is the standard of care for determining liver failure. more often as necessitated by clinical course; may be reduced in patients who are stable (i.e. outpatient) and whose biochemical markers have improved

Table 3:

Omegaven® Possible Adverse Events

CLINICAL			
GRADE I (MILD)	**GRADE II (MODERATE)**	**GRADE III - SAE (SEVERE)**	**GRADE IV - SAE (POTENTIALLY LIFE THREATENING/ DEATH)**
Phlebitis	**Hypotension**	**Bowel obstruction**	**Uncontrolled bleeding**
Fever	**Hypertension**	**Sepsis syndrome**	**Anaphylaxis**
Fishy taste	**Urinary tract infection**		**Shock**
Chills	**Poor growth**		**Death**
Flushing	**Priapism**		
Cyanosis			
Nausea/Vomiting			
Dehydration			
Rash			
LABORATORY			
Hyperglycemia	**Anemia**	**Sepsis**	**Coagulopathy**
Hypertriglyceridemia	**Leukopenia**		
Essential fatty acid deficiency	**Thrombocytopenia**		
Electrolyte abnormalities	**Abnormal liver function tests**		
	Positive urine culture		