CENTER FOR DRUG EVALUATION AND RESEARCH

TITLE:

Compassionate Use of an Intravenous Fat Emulsion Comprised of Fish Oil (Omegaven) in the Treatment of Parenteral Nutrition Induced Liver Injury

APPLICATION NUMBER:

210589Orig1s000

***Date*: 01/29/2021**

Part B: Experimental Design and Protocol – **ALL APPLICANTS MUST COMPLETE THIS FORM**

Please refer to the INSTRUCTIONS MANUAL for assistance in completing the protocol application. The instructions manual is available on the CCI website, under '*Forms-New Protocol/3 Year Rewrite*'.

You may use this web-based form to develop your protocol, or you may insert the protocol and experimental design from another source. Either way, please ensure the final protocol covers the elements listed below as they apply to the research before submission to the CCI.

Part B should be written to reflect the research as it will be conducted at or through Children's Hospital.

Further information may be obtained by referring to **the polices and procedures on the CCI website**

Please provide a brief summary or abstract of this research protocol.

In the United States, patients dependent upon parenteral nutrition (PN) receive parenteral fat 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. 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 PN associated liver disease. We hypothesize 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 resulting in steatotic liver injury. We further hypothesize that a fat emulsion comprised of omega-3 fatty acids (i.e., fish oil) such as Omegaven® would be beneficial in the management of steatotic liver injuiry 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, we hypothesize that 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 fat 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.

1. Specific Aims /Objectives

1. To determine the safety profile of an intravenous omega-3 fat emulsion (Omegaven®)

Hypothesis for Aim 1:
1.1 – After starting Omegaven® on PN, the rate of fatty acid deficiencies and imbalances will be as low as before Omegaven®. Also, the rate of triglyceride events > 400 mg/dL with Omegaven® will be similar to that seen with PN administered with soy oil IFE (conventional emulsion, i.e., Intralipid®).
1.2 – PN containing Omegaven® will be safe for patients with respect to the risk of unexpected bleeding, coagulopathies, and other adverse events.
1.3 – PN containing Omegaven® will promote more short-term growth and development than conventional fat emulsions.

2. To determine if established PN associated liver disease can be reversed or its progression halted by using a parenteral fat emulsion prepared from fish oil as measured by normalization of serum levels of hepatic enzymes and bilirubin.

Hypothesis for Aim 2:
2.1 – Our primary hypothesis is that, after reaching bilirubin levels > 2 mg/dL, patients receiving Omegaven® will reach a bilirubin level ≤ 2 mg/dL faster than patients receiving conventional fat emulsions. Additionally, while patients receiving Omegaven™ will experience a decrease in their levels of bilirubin and other hepatic enzymes over time, patients receiving conventional emulsions will maintain high levels of bilirubin and other hepatic enzymes over time.
2.2 – Patients with surgical gastrointestinal disease and cholestasis will have better clinical hepatic outcomes than patients receiving conventional emulsions.
2.3 – Since patients receiving Omegaven® will have improved immune function, they will have a lower infection rate then patients receiving conventional fat emulsions.
2.4 – Due to a better general hepatic condition, patients receiving Omegaven® will also experience lower occurrence of liver transplant, death from hepatic associated causes, and blood transfusions.

2. 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 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 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 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 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 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.

3. Preliminary Studies/Progress Report

Animal Studies

In our initial studies, we hypothesized that the development of PNALD may be dependent on both the route and quantity of fat administration and that omega-3 fatty acids would prevent or reduce *de novo* lipogenesis and the subsequent liver injury independent of the route of administration. Specifically, we characterized a previously established murine model of PN-associated liver injury to investigate whether enteral lipid administration would protect against the development of steatohepatitis in PN-dependent

animals. This murine model of enteral PN-induced 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. In this study we 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 formula mixed at our institution 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. We recognize that the model may not completely match the clinical, human, setting of intravenous PN-administration; however, our goal was to produce a fatty liver with biochemical evidence of injury. Please refer to the attached paper from *Pediatric Research* that discusses our findings in greater detail.

In a second set of experiments, the same murine model was used to determine whether Omegaven® (Fresenius- Kabi, Bad Homburg, Germany), a commercial fish oil fat 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, arachidonic 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. Our experience to date, as discussed below, 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 (1ml) to a maximum of 0.2 (2ml) /kg body weight. The infusion rate used did not exceed 0.5ml/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

Pediatric experience with Omegaven® is limited to 2 unpublished clinical trials (see appendix). 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.

Results of Prior Patient at Children's Hospital Boston

The only prior use of Omegaven® for monotherapy, both in the United States as well as well as abroad, is limited to its use in an adolescent male in 2002 (IRB approval # E02-070-010) who required a soy free form of parenteral fat emulsion for the treatment of essential fatty acid deficiency. In that instance, therapy was started at 0.2gm/kg/day and advanced to 0.67 gm/kg/day. He remained on Omegaven® a total of 57 days. His essential fatty acid deficiency corrected and he did not experience any adverse events during his course of therapy that could be attributed to the use of Omegaven®. Please refer to the attached case report summarizing this experience.(30)

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 c-reactive protein (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 27 months.

Since that time, an additional 55 patients have been treated with Omegaven®. As of August 9, 2007, no patient receiving Omegaven® has died of PN associated liver disease.

Summary of patients treated to date is described in the supporting documentation.

A preliminary meeting with the FDA occurred on Thursday, February 9, 2006 to discuss the planned randomized, controlled trial comparing conventional therapy (i.e., Intralipid®) to Omegaven®. An Investigational New Drug (IND) application was granted on December 13, 2006 (IND 73,488).

4. Design and Methods

a. Study Design

Assessment of the effect of treatment will be based on a non-randomized, open-labeled, prospective study of intravenously administered Omegaven® fat emulsion to determine safety and preliminary efficacy in the treatment of PN associated liver injury. This treatment group will be compared to a group based on historical controls, i.e., a subset of patients (those whose direct bilirubin levels was ever > 2 mg/dL) previously studied by Andorsky et al.(31) This study included neonates treated between 1986 and 1996 who depended on parenteral nutrition for at least 90 days after surgical therapy for congenital or acquired intestinal diseases. Our study will primarily follow the patients included in Andorsky et al. study from 2 months before direct bilirubin first reached a level > 2 mg/dL (baseline date) until 2 months after patients either reached 3 consecutive bilirubin levels ≤ 2 mg/dL or reached one bilirubin level ≤ 2 mg/dL and were weaned from PN died, or underwent a liver transplant. In our exploratory analyses, we will include the entire available follow-up time in Andorsky et al. dataset for each patient.

b. Patient Selection and Inclusion/Exclusion Criteria

Omega-3 Fat Emulsion (Omegaven®)

After the diagnosis of PNALD is made, patients who are followed by the Clinical Nutrition Service (CNS) or General Surgery Program, in conjunction with the patient's primary physician, will contact Dr. Puder or Dr. Duggan and an evaluation will be performed. Cases may also include referrals of patients with PNALD from other healthcare facilities or self-referrals. 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. This form 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 fulminate liver failure. The study population of this protocol is limited to patients felt to fulfill any one of the following conditions:

a) The patient will be PN dependent and at risk for significant hepatic injury due to prolonged use of parenteral nutrition.

b) Have significant hepatic dysfunction due to parenteral nutrition despite utilization of all conventional therapies.

Inclusion Criteria:

1. Patients will be PN dependent (unable to meet nutritional needs soley by enteral nutrition) and are expected to require PN for at least another 30 days
2. Patients considered eligible for study participation must have parenteral nutrition associated liver disease (PNALD) as defined as a direct bilirubin of $\geq$ 2 mg/dl or currently on Omegaven through another protocol. Other causes of liver disease should be excluded. A liver biopsy is not necessary for treatment.
3. Direct bilirubin > 2.0 mg/dl, or already on Omegaven through another protocol.
4. Signed patient informed consent.
5. The patient must have utilized standard therapies to prevent the progression of his/her liver disease including surgical treatment, cyclic PN, avoiding overfeeding, reduction/removal of copper and manganese from PN, advancement of enteral feeding, and the use of ursodiol (i..e., Actigall®).

Exclusion Criteria:

1. Pregnancy
2. Other causes of chronic liver disease (Hepatitis C, biliary atresia, and alpha 1 anti-trypsin deficiency,)
3. Enrollment in any other clinical trial involving an investigational agent (unless approved by the designated physicians on the multidisciplinary team)
4. The parent or guardian or child unwilling to provide consent or assent

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). Such causes may not be known at the time of enrollment and will not preclude them from continuing in the study. For the sake of statistical analysis, however, these patients will be excluded although all data will be collected and reviewed.

Screening Procedures

All patients receiving parenteral nutrition are followed by the Clinical Nutrition Service. Eligibility for the trial will be discussed on rounds. 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. A similar process will be utlized for self-referrals and potential patients referred from distant healthcare facilities.

Soybean based Fat Emulsion (Intralipid® and/or Liposyn®)

The conventional PN comparison group will be selected from patients previously studied by Andorsky et al.(31) We will study the subset of those patients whose recorded direct bilirubin was ever > 2 mg/dL. Information about these patients will be extracted from the Excel database used for this study and provided to us by the study's Principal Investigator, Dr. Christopher Duggan. A request for research limited to the use of medical records/charts and computer databases was submitted and approved by the Committee on Clinical Investigations on January 17, 2007 (M07-01-0030).

Inclusion Criteria:

Andorsky et al. reviewed medical records of patients who were born at Children's Hospital Boston from 1985 to 1996 and who received a diagnosis of short bowel syndrome at most 30 days after birth (in the neonatal period). Short bowel syndrome was defined as dependence on PN for at least 90 days for diagnosis resulting from congenital intestinal malformations and/or intestinal resection.

Exclusion Criteria:

Patients with incomplete medical records (10 patients briefly seen for a second opinion) were excluded from the Andorsky et al. study. For our study, we will further exclude the subset of patients whose direct bilirubin was never > 2 mg/dL at any time during their follow-up times.

Follow up Study Utilizing Contemporary Historical Controls
A second analysis will be done using more contemporary historical controls from patients receiving conventional PN This will include 50 patients (approximately 10 per year) retrospectively enrolled and previously treated with soybean based emulsions from 1999-2004. Subjects will be selected among patients with surgical gastrointestinal diseases and will have been expected to need PN for 30 days or more at the beginning of PN administration. For the retrospective soybean cohort, to make their selection process comparable to the prospectively enrolled Omegaven® cohort, we will apply the inclusion criteria to the records at moment that cholestasis develops (i.e., direct bilirubin $\geq$ 2mg/dL) making no assumptions based upon the outcomes of their actual PN course. Unlike prior analyses comparing Omegaven® treated patients with PNALD with those receiving only soybean fat emulsions, this cohort is expected to be more contemporary with less variability in the standards of care as the study period only covers 4 years rather than 12 year period examined by Andorsky et al. A request for research limited to the use of medical records/charts and computer databases was submitted and approved by the Committee on Clinical Investigations on July 25, 2007. (M07-07-0312).

Inclusion Criteria:
1) Age < 2 years; 2) Be PN dependent (unable to meet nutritional needs solely by enteral nutrition); 3) Present PNALD, as evidenced by two consecutive direct bilirubin $\geq$ 2.0 mg/dL; 4) Have failed standard therapies to prevent the progression of his/her liver disease that may include surgical treatment, cyclic PN, avoiding overfeeding, reduction/removal of copper and manganese from PN, advancement of enteral feeding, and the use of ursodiol (i..e., Actigall®); 5) At the time the diagnosis PNALD is made, the patient is expected to continue PN at least an additional 30 days.

Exclusion Criteria:

Other known causes of chronic liver disease (hepatitis C, cystic fibrosis, biliary atresia, and alpha 1 anti-trypsin deficiency).

c. Recruitment Methods

Omega-3 Fat Emulsion (Omegaven®)
Patients in the proposed trial will be referred from the Children's Hospital Surgical Department, the NICU, or Clinical Nutrition Service. Patients with PNALD may also be referred from other healthcare facilities by their physicians or be self-referred. Approximately 5-10 patients/year are diagnosed with severe PN associated liver injury at CHB. The Principal Investigator (Dr. Puder) or Co-investigator (Dr. Duggan) will discuss treatment options including study treatment with the patient (and parents or legal guardians in the case of a minor). Informed consent for participation in the study will only be obtained from these

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.

ii. WHAT recruitment methods and materials (e.g. posters, fliers) will be used? - *attach all materials*

none

iii. WHO will be responsible for subject recruitment?

No patients are recruited for this study. For patients that are referred for further consideration, the Principal Investigator (Dr. Puder) or Co-investigator (Dr. Duggan) will discuss treatment options including study treatment with the patient (and parents or legal guardians in the case of a minor).

Soybean based Fat Emulsion (Intralipid® and/or Liposyn®)

Subjects for the Andorsky et al. study were identified based on: 1) International Classification of Diseases, Ninth Revision code of 579.3 (post-surgical malabsorption, commonly used to code short bowel syndrome); 2) review of the list of patients receiving PN at home who were followed by the Clinical Nutrition Service at Children's Hospital Boston; and 3) survey of attending surgeons, gastroenterologists, and nutrition physicians at Children's Hospital Boston.

Soybean based fat emulsion patients will initially be identified by the Clinical Nutrition Service, Pharmacy billing, and clinical laboratory records. We will at first seek all patients that received PN between 1999 and 2004. Subjects will then be selected based on ever presenting with cholestasis (based on direct bilirubin records). After that, we will apply the inclusion criteria to the patient's record at the moment that cholestasis is characterized. To further assure comparability between the two groups, we will also base identification of patients for inclusion in the control group by: 1) International Classification of Diseases, Ninth Revision code of 579.3 (post-surgical malabsorption, commonly used to code short bowel syndrome); 2) review of the list of patients receiving PN at home who were followed by the Clinical Nutrition Service at Children's Hospital Boston; and 3) review of the list of patients followed by the Center for Advanced Intestinal Rehabilitation (CAIR) Team at Children's Hospital, Boston.

d. Description of Study Treatments or Exposures/Predictors

TREATMENTS™

Omega-3 Fat Emulsion (Omegaven®)

Bottles containing 50mL or 100 mL of 10% Omegaven® will be purchased from International Pharmacy of Hamburg, Germany or directly from the manufacturer. Approval was received from the FDA in March 2007 to allow for billing of Omegaven®. In the event that third party coverage is not available Children's Hospital, Boston will cover all drug costs for patients enrolled in this protocol. Omegaven® is manufactured by Fresenius Kabi AG, Bad Homburg v.d.h, Germany. Omegaven® is formulated as an emulsion from fish oils

While inpatient, the emulsion for all patients will be repacked into syringes to allow for administration via syringe pump. However, if patients require over 100ml (10g) of Omegaven®, they will receive the medication via bottles. If patients are to be discharged home on Omegaven®, all doses will be administered from the original manufacturer's container.

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 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 study, all used and unused Omegaven® will be accounted for. If expired, the remaining drug supplies will be destroyed.

Details of Omegaven® Administration

After baseline labs are obtained (Tables 2 and 3), therapy with Omegaven® will be initiated at the goal dose of 1 gram /kg/day and is infused over 8-24 hours, so long as the infusion rate does not exceed 0.15g/kg/hour. Omegaven® will be infused intravenously through either a central or peripheral catheter alone or in conjunction with parenteral nutrition. If additional fat calories are needed, they will be provided via the enteral route. The same standards of care provided to all patients receiving parenteral nutrition solution will be followed. Routine nutritional monitoring is described in Table 3.

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 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. The DSMB will also be notified.

Orders for Omegaven® will be written on a CHB PN order form and must contain the following data elements:

- Total daily dose to administered in mL
- The hourly infusion rate (total daily dose ÷ the number of hours to be infused)

Prior to the administration of each Omegaven® dose, two nurses will check the dose dispensed against the physician's orders and verify that the infusion pump settings (hourly rate, volume to be infused) are correct before the infusion is started.

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. Per Infection Control, source containers must be changed every 12 hours and unused product discarded. Omegaven® may be infused through a 1.2micron inline filter.

Dose Modification

Lipid Intolerance

If lipid intolerance 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 lipid intolerance should be considered and addressed (drugs, renal disease)

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

High Glucose Infusion Rate

Subjects with a high glucose infusion rate (GIR) will have a dose increase up to 1.5 grams/kg/day to allow for a reduction in PN calories from carbohydrates at the discretion of the Omegaven study team and the nutrition service.

Duration of Therapy

Patients will remain on Omegaven® until weaned from PN. Patients may continue monotherapy with Omegaven® as an additional source of calories after the dextrose/protein portion of PN is discontinued

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.

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. Some potential interventions that can be used include:

Situation	**Possible Solution**
Loss of central venous access	Administer via peripheral route
Fluid restriction	Consult with pharmacy to concentrate PN, medications to allow for administration
Limited access, need to administer incompatible medications	Stop Omegaven® infusion, flush catheter with either NS or dextrose, administer incompatible medication, flush catheter, resume infusion; may be necessary to infuse Omegaven® over 8 -24 hours. Multiple syringes should be used so as to keep maximum hang time of Omegaven® source container less than 12 hours) Regardless of the infusion time, **the infusion rate cannot exceed 0.15g/kg/hour.**

Discontinuation of Therapy

Patients will continue to be followed by the Center for Advanced Intestinal Rehabilitation (CAIR) Program upon discontinuation of therapy with Omegaven® for a minimum of 2 months after the treatment is stopped.

Resumption of Therapy

For patients who have been off the protocol more than 1 year, in the event that the patient must receive intravenous fat emulsion, treatment with Omegaven® will resume only if the patient shows evidence of PN liver damage (elevations in direct bilirubin ≥2 or pathology findings consistent with cholestasis). Otherwise, the patient will be treated with conventional fat emulsion.

Soybean based Fat Emulsion (Intralipid® and/or Liposyn®)

Subjects in the Andorsky et al cohort received one of two commercially available intravenous fat emulsions (IFE), Liposyn® II or Intralipid®. IFE is provided as an oil-in-water emulsion derived from egg phospholipids, soybean or safflower oils and glycerol. Although three concentrations are commercially available (10, 20, 30%) only the 10 and 20% concentrations have been approved for use in children. Both Liposyn® II and Intralipid® contain soybean oils. Table 1 summarizes the composition of both products.

Details of IFE Administration

Regardless of the product used, doses less than 96 ml/day were repacked into syringes to allow for administration via syringe pump. Doses greater than 96ml/day were dispensed in the original manufacturer's container. If patients were discharged home on either IFE, all doses were administered from the original manufacturer's container.

For either brand, IFE was typically initiated at a low rate and advanced as tolerated. In the Andorsky et al cohort, a typical starting dose for VLBW infant was 0.5 - 1 g/kg/day that was advanced in increments of 0.5 g/kg/day until a goal of 3 g/kg/day is reached, provided that it did not exceed 60% of total calories. Larger neonates usually received initial doses of 1 - 2 gm/kg/day. To improve tolerance, IFE was infused over 24 hours. Prior to initiating fat emulsions lipids, serum triglyceride levels were checked and then monitored to assess tolerance. Tolerance was typically defined as triglyceride levels < 200 mg/dL. Once a goal regimen was reached (not to exceed 60% of total calories) serum triglycerides were checked weekly.

Dose Modification

As most serum triglyceride levels are checked while IFE was infusing, it was common practice for patients who appeared unable to tolerate IFE, to hold the IFE infusion for 4 hours and have the serum triglyceride levels checked immediately before resuming the infusion. In most instances, serum triglyceride levels would drop to a desirable range. If not, no further dosing increases were made or every other day administration was considered.

Although some cases of lipid intolerance were attributable solely to excessive amounts of intravenous fat emulsions, many patients receiving PN had other reasons to have elevated serum triglycerides including acute phase stress response and sepsis. Some practitioners opted to reduce the dose or discontinue IFE during acute episodes of sepsis, RDS, thrombocytopenia, or severe hyperbilirubinemia (i.e., approaching exchange level). Provided that the serum triglyceride was < 200 mg/dL, a minimum of 2-4 % of non-protein calories was administered as fat (approximately 0.5 g/kg/day) to provide sufficient essential fats to prevent essential fatty acid deficiency.

Because both Intralipid® and Liposyn® II are isotonic, both could be infused through either a central or peripheral line. Both products are compatible with parenteral nutrition solutions and were co-infused via y-site. Source container hang times varied during this period, and IFE was either infused from a single container over 24 hours or the container was changed every 12 hours per CDC recommendations. Also during this period, the administration method of PN changed. Prior to 1999, standard 0.2 micron inline filters were used routinely and only PN but not IFE could be infused through them (IFE was infused via y-site beneath the filter). After 1999, 1.2 micron filters became the standard inline filter, allowing for IFE to be filtered along with the PN solution.

Duration of Therapy

Patients remained on either Liposyn® II or Intralipid® until weaned from PN.

Discontinuation of Therapy

Patients at risk for malnutrition or resumption of PN were typically followed by the Clinical Nutrition Service for several months following discontinuation of PN.

ADDITIONAL PREDICTORS OF INTEREST

Since decisions about starting Omegaven® administration will follow a compassionate protocol, we expect that patients receiving Omegaven® will present more severe liver disease than the controls from the historical cohort. Therefore, to correct confounding biases, we anticipate the need to adjust for potential predictors of liver outcomes at baseline. Baseline will be defined as: the date that treatment starts for Omegaven® patients and on the date that patient reached bilirubin levels > 2 for soybean based fat emulsion patients.

The following predictors of liver disease will be considered:

- Baseline direct bilirubin levels.
- Diagnosis of Necrotizing Enterocolitis (vs. any other disease)
- Gender (male vs. female)
- Age (≥ 8 months vs. < 8 months)
- Gestational age
- Birth weight
- Race

To assess patients comparability, we will also descriptively explore trends in direct bilirubin level before the beginning of follow-up (start of treatement date for Omegaven® patients and date in which direct bilirubin level raised to > 2 mg/dL for control patients)

Subgroup Analysis

With exploratory purposes, we will describe safety and/or efficacy of Omegaven® in subgroups of patients including younger (vs. older) patients at baseline, patients who presented with infections (vs. who did not),

who underwent transfusions (vs. who did not), and who underwent operations while receiving PN (vs. those who did not).

Secondary Fatty Acid Analysis on Red Blood Cell Membranes

Utilizing the waste we draw off central line blood draws and discard for our current protocol, it is our intention to store this usually discarded sample without any identifiers and use them for a fatty acid analysis on the red blood cell membrane. As a routine part of our protocol we look at "free fatty acids" in the blood but this only yields limited information. This analysis will allow us to examine the fatty acid composition of the red blood cell membranes which is significantly influenced by the ratio of dietary 3 to 6 fatty acids.

We plan to test de-identified discarded blood samples for lipid derivatives of omega-6 and omega-3 fatty acids. The measurement of the small molecules involved in lipid pathways is termed "lipidomics." Insight into changes in lipid production may be critical to understanding the pathophysiology of parenteral nutrition-associated liver disease and understanding the therapeutic benefit of fish oil-based lipid emulsions. We would like to send **de-identified** discard blood to a collaborator at UC-Berkeley who can perform a "lipidomic" analysis of the serum. This analysis details the lipid mediator composition in the blood. The discard blood (specifically serum) will be sent to Dr. Karsten Gronert, Associate Professor of Vision Science and Optometry; Solon M. and Pearl A. Braff Chair in Clinical Optometric Science; Center for Eye Disease & Development, UC Berkeley. Dr. Gronert is one of the few investigators in the world who has the expertise to quantify some of the specific lipid mediators of interest in this study.

e. Definition of Primary and Secondary Outcomes/Endpoints

Generally, primary safety analyses will be based on time from baseline or 30 days after baseline until two months after patients first reached direct bilirubin levels < 2mg/dL. Baseline will be defined as information collected at the date that treatment starts for Omegaven® patients and on the date that patient reached bilirubin levels > 2 for soybean oil fat emulsion patients. Information on mortality and transplant will be collected during the whole treatment with Omegaven® and during the whole period for which we have data available in the Andorsky et al. dataset. Primary efficacy analysis will include time from baseline until the patient normalizes bilirubin (presents three consecutive direct bilirubin ≤ 2 mg/dL or a direct bilirubin ≤ 2 mg/dL and weaned from TPN). With exploratory purpose, we will also describe the curve of the several markers for the entire period that Andorsky et al. recorded data.

Outcome/Endpoints

1. Treatment safety

Our primary outcome for treatment safety will be based on patient's essential fatty acid profile. We will compare patients before treatment with Omegaven® started and after treatment started (one month after treatment started until treatment stopped) with respect to the frequency with which triene/tetraene ratio > 0.2 at any time. We will also compare the occurrence any event of of hypertriglyceridimia (serum triglyceride > 400mg/dL) between Omegaven® and soybean oil fat emulsions. Primary analyses for these and all other safety outcomes will be based on a follow-up time for Omegaven® and soybean oil fat emulsions starting 30 days after baseline, i.e., 30 days after treatment started for Omegaven® patients and 2 months after the first direct bilirubin level < 2 mg/dL was recorded. We will also explore comparisons including the time from baseline until the end of follow-up period.

Additional comparisons across treatment periods for subjects receiving Omegaven® will be aimed to assess occurrence of spontaneous bleeding (e.g., unexplained bruising, oozing from gums/incision sites), and maximum triene/tetraene ratio, minimum platelets, and maximum international normalized ratio (INR). trends in pre-albumin (age standardized levels). We will also explore trends in coagulopathies based on curves of platelets, prothrombin time (PT), partial thromboplastin time (PTT) over time, and INR. We will also describe the rate with which INR ratios were > 2 (number of days/follow-up time), as a marker of coagulopathies.

Additional comparisons between Omegaven® and soybean oil fat emulsion groups will be performed with regards to rate in which albumin is > 3 g/dL, maximum triglyceride level, rate of blood stream infections (number of positive blood cultures/follow-up-time under PN after baseline), rate of central venous catheter (CVC) infections (number of CVC infections/follow-up time and number of gram positive CVC infections/follow-up time), and occurrence of anaphylatic reactions after baseline.

Nutritional outcomes between Omegaven® and soybean oil fat emulsion groups that will be compared include changes in weight- and height-for-age Z-scores from baseline to 10% PN or cessation of PN..

We will describe trends over time for all outcomes associated with fatty acid profiles (including triene/tetraene ratios, triglycerides, total omega-6 fatty acids, total omega-3 fatty acids, total saturated, total monounsaturated, and total polysaturated fatty acids). Specific fatty acids such as arachidonic, palmoteleic, palmitic, oleic, stearic, and linoleic fatty acids will also be evaluated and described. Also, for exploratory purposes, we will compare the trend in weight- and height-for-age Z-scores between both groups.

2. Omegaven®

3. The patient will complete treatment with Omegaven® in this 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.

f. Data Collection Methods, Assessments and Schedule

Omega-3 Fat Emulsion (Omegaven™)

Data will be collected by the PI (MP), the managing co-investigator (KG), and the clinical coordinator with the assistance of the nursing unit liaisons and research assistants in Dr. Puder's laboratory Hospital charts will be reviewed for pertinent clinical information. Results of liver biopsies and blood chemistries will be obtained from PowerChart within the Cerner computer system at CHB. 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.

Soybean based Fat Emulsion (Intralipid® and/or Liposyn®)

Data will be extracted from the Excel spread sheet used to store data of the Andorsky et al. study. Additionally, we will obtain information about date of birth (to estimate age at each visit and nutritional safety outcomes) and blood transfusions in Power Chart within the Cerner computer system at CHB. In the original study performed by Andorsky et al., data was abstracted from charts, nursing flowsheets (for nutritional intake data), and outpatient visit notes in two week intervals.

g. Study Timeline (as applicable)

This study 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. The investigators proposal to the Orphan Products Grants Program of FDA submitted in spring 2007 which was accepted.

h. Adverse Event Criteria and Reporting Procedures

Adverse events (AEs) will be assessed and reported from the time of the first Omegaven® infusion until exit from the study in accordance with CHB Committee on Clinical Investigations (CCI) reporting requirements. In particular, the patient will be observed during and shortly after Omegaven® administration for the occurrence of anaphylactic or allergic reactions. Other expected adverse events include death, blood stream infection; transfer to ICU for treatment of respiratory distress or homodynamic instability; re-hospitalization for treatment of blood stream infection, dehydration, electrolyte abnormalities, catheter malfunctions, bowel obstructions, and urinary tract infection. Unexpected adverse events will also be assessed and reported in compliance with the CHB CCI requirements. 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 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.. Patients with anaphylactic or allergic reactions will not continue Omegaven® treatment.

Any serious or unsuspected adverse events will be reported to the Committee on Clinical Investigation (CCI) and the FDA within 72 hours.of the occuranceof being known, or immediately if the event is fatal or life threatening as per Children's Hospital Policy on Adverse and Unexpected Events and Unanticipated Risks to Research Subjects and Others. This will be done in person, by telephone, or email, and by completion of the CCI's form for adverse/unexpected event reporting.

Adverse events are detected by CHB acute care 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 CHB staff are reported to the Principal Investigator immediately by telephone or pager, and subsequently to the appropriate board or committee.

A Committee of the Study Investigators (Drs. Puder, Gura, and Duggan) will be responsible for assuring that adverse event reporting requirements are actually met. The Investigator Committee will meet not less than monthly to conduct clinical case reviews of all patients receiving Omegaven® to review recruitment data, adverse events and protocol deviations; and to evaluate overall safety of Omegaven® therapy. CHB Staff dieticians caring for Omegaven® patients will participate in the Investigator meetings as necessary. Any patients who have agreed to participate in the trial, but who have not yet undergone intervention, will be informed of adverse events. A revised consent document will be submitted to the CCI with the adverse event form for reviewand approval. All adverse events will be classified by the Principal Investigator as definitely, probably, possibly, or unrelated to administration of study drug

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

a) Toxicity considered unacceptable by the Principal Investigator
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 Principal 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 from the protocol, study staff 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. Data Management and Statistical Analysis

a. Data Management Methods

Overview

All clinical and laboratory research data will be abstracted from source documents (medical records) and recorded and maintained on study specific case report forms (CRF). These CRFs will be stored within individual subject binders in accordance with Good Clinical Practice Standards and FDA requirements. Study materials will be kept in the Principal Investigator's locked office and access will be restricted to authorized study staff only. Subject confidentiality will be maintained by recording subject-specific data using a unique confidential study identifier.

Staff from the Clinical Research Program (CRP) at Children's Hospital will collaborate with the Study Investigators (Drs. Puder and Gura) and Study Coordinator to manage the study data. CRP staff has extensive experience in the design, conduct and management of clinical trials data.

Protocol Management and Protocol Status

The data management system for the Omegaven® Compassionate-Use protocol is currently programmed as Redcap, a free and secure web-based application designed to support electronic data capture for research studies.. Redcap provides a simple point-and-click interface to create web-based case report forms with the ability to customize real-time data entry validation (e.g. for data types and range checks), maintain project audit trails, export project data to advanced statistical software packages and assign different levels of data access for each member of the research team. Redcap will support cross-sectional and longitudinal research designs. Redcap was developed by a multi-institutional consortium initiated at Vanderbilt University. Each institution is responsible for hosting a separate instance of Redcap in a manner that is consistent with all local policies and procedures. This configuration allows the host institution to define Redcap data security policies, data backup schedules, data retention plans and involvement of necessary departments in the Redcap project creation process (IRB, Human Subject Protection Organization, Clinical Research Center, Office of Business Conduct, etc…) Only authorized users are permitted to access data and daily server backup procedures are executed to ensure system reliability and data recovery.

b. Quality Control Method

Study Conduct

Several QA procedures will be implemented to promote and monitor compliance with study protocols and procedures and allow timely reporting of protocol deviations.

1. Case Report Forms (CRFs): An offical document review and sign-off process will be established to guarantee all critical primary and secondary outcome measures are included on the CRFs. In additon, CRFs will be designed to incorporate clearly specified definitions and simple instructions to data collectors to minimize data collection errors.

2. Procedures Manuals: Written data collection, data manamgment and data entry procedures will emphasize timely data capture in relation to real time events including actual clinical and laboratory measurements.

3. Clinical Data Management System:
The REDCap clinical data management system will be used for data entry. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

4. Staff Training: A training program will be developed and delivered to CHB clinical staff to review the aims of the Omegaven® compassionate-use protocol, review standard care clinical protocedures, protocol-specific clinical and laboratory measurement procedures, and procedures for when and how to contact the PI. Training will be coordinated by the Study Coordinator and delivered in whole or in part by the PI (MP) and Co-PI (KG). Where possible, training components will be offered as Net Learning Modules.

5. Omegaven® Administration: CHB nursing staff will be instructed to adopt the following special procedures for Omegaven® administration to prevent administration errors for patients residing in CHB clinical care units, e.g. NICU, MICU, etc.

- The dose, rate, and pump settings will be confirmed by 2 nurses prior to the start of the infusion.
- The double check will be documented on the flow sheets, power chart or eclypsys in the same manner as the documentation required for blood product administration.
- The physician orders will be written beyond the standard care requirement to include the primary Omegaven® dose calculations of total volume to be infused over 8-24 hours as well as the hourly infusion rate so that no primary calculations will be required by the nursing staff.

A limited tolerance for deviations in Omegaven® dosing will be allowed to accommodate expected variations that commonly occur when providing standard clinical care of pediatric patients receiving nutritional supplements including essential fatty acids. For example, in cases where patients are also prescribed medications that are incompatible with Omegaven®, (e.g. morphine) dosing may vary up to a 1.5 hour dose equivalent. Omegaven® infusion may also be stopped / postponed when a patient goes for special diagnostic studies or procedures or therapeutic treatments. An Omegaven® dose range will be established for protocol deviation reporting such that Omegaven® dosing will be set at target (1 gram of Omegaven® per kilogram of body weight per day) plus or minus a 1.5 hour dose equivalent. Dosing variations that exceed the tolerance range will be reported to the CCI as protocol deviations.

6. Specimen Collection/Laboratory Testing / Laboratory results data capture:
All laboratory studies captutred for the Omegaven® compassinate use protocol are considered standard care laboratory tests for this patient population. No additonal QA procedures will be established beyond the QA procedures already established as CHB standard operating procedures for patient care, specimen collection, processing, storage, shipping and resuts reporting. If specimens are not drawn on schedule, if specimen volume is insufficient, or if specimen are contaminated or destroyed such that laboratory test results are missing or deemed invalid for any reason, laboratory values will be recorded as missing on the laboratory CRFs and in the CDMS. If any of the following laboratory values are missing at baseline or for 2 consecutive cycles, a report of a protocol deviation will be reported to the CCI and DSMB:

- Serum triglycerides;
- Coagulation labs, PT, PTT, INR;
- Essential Fatty Acid Profile;
- Direct and total bilirubin values;

Re-training of clinical, research and/or labortory staff will be conducted if safety labs or primary outcome lab values are missing on two consecutive occasions.

7. Data Capture:
The study nurses will abstract the medical records and complete the CRFs. The study coordinator will provide a careful QC visual inspection of the CRFs prior to submiting them for data entry. CRFs will be inspeced for completeness and out of range values. The Research Coordinator will complete all data entry. The selected CRFs will undergo 100% verification against source documentation (medical records, laboratory data, etc).

Dispensing of Study Drug

Pharmacy: Pharmacy dispensing records will be reviewed by the CRP Study Monitor on a montly basis to ensure adherence with procedures for dispensing Omegaven®

Legal and Ethics Requirements

This study is being conducted under an FDA Investigational New Drug Application. As such, FDA regulations 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 research binder; a copy will 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 study coordnator 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 five (5) years following discontinuation of the study.

Data Quality and Completeness

Allowable ranges were created for each variable of interest and records outside of those ranges were checked.

c. Data Analysis Plan

Using graphical methods (including boxplots) and descriptive statistics, we will assess assumptions required for validity of statistical methods and presence of outliers. Continuous variables will be summarized via means (and standard deviations) or medians (and interquartile ranges, when appropriate. When appropriate varibles will be transformed.

Primary analyses of the primary outcome will be be based on the intention-to-treat analysis i.e., patient will be considered receiving either omegaven® or soybean based emulsions throughout the whole follow-up period, regardless of temporary discontinuation of treatment due to infections or other causes.

Analysis of Baseline Characteristics

For statistical pursposes, baseline values will be defined as the last measurement before starting to administer Omegaven® for patients, in the treatment group, and as the measurement taken when a patient first had a direct bilirubin level > 2 mg/dL recorded, in the historical control group. Descriptive statistics for all baseline relevant risk factors will be summarized for Omegaven® (omega-3 based fat emulsion) and historical control (soybean oil fat emulsion) groups. Associations between categorical predictors and Omegaven® vs. soybean oil fat emulsion groups will be tested through chi-square tests. Associations between continuous predictors and treatment groups will be studied through means (and standard deviations) and t-tests, or medians (and interquartile ranges) and Wilcoxon tests, when appropriate.

Analysis of Safety and Tolerability of Omegaven®

All primary safety and tolerability analyses will be based on descriptive statistics. In secondary analyses, we will also assess the statistical significance of differences. Some safety and tolerability outcomes will be measured only in the Omegaven® group. For those, we will compare results before starting PN with Omegaven® (while receiving PN with soybean oil fat emulsions) with after starting PN with Omegaven®. The period receiving Omegaven® will start to be counted 30 days after beginning PN with Omegaven® for the main analysis. Outcomes measured in the Omegaven® and soybean oil fat emulsion groups will be described separately for each of those groups for a period starting 30 days after baseline, i.e., 30 days after starting PN with Omegaven®, for the treatment group, and 30 days after bilirubin > 2 mg/dL, for the soybean oil fat emulsion group.

Primary outcomes measured only in the Omegaven® group will include whether the triene/tetraene ratio was ever > 0.2 during the intervention period and whether the INR was ever > 2. Secondary outcomes measured only on the Omegaven® group will include platelets, prothrombin time (PT), partial thromboplastin time (PTT), and other components of the fatty acid profile. Analysis of all categorical outcomes will be based on proportions and of all continuous outcomes will be based on means or medians of the individual mean, maximum or minimum values, as appropriate, during the respective follow-up period. Comparisons between periods (pre and post-treatment) will be performed based on paired tests, parametric or non-parametric, as appropriate. We will also explore trends over time (e.g., decreasing for INR and increasing for pre-albumin) and estimate p-values via regression models using generalized estimating equations or random effects to account for within subject correlations. When describing outcomes over time, we will explore the effect of predictors of poor hepatic outcomes, such as use of antifungal agents (e.g.., amphotericin) and antidiarrheal agents (e.g., loperamide), on potential spikes.

Primary outcomes measured in the Omegaven® and soybean based fat emulsion groups will include whether triglycerides were ever > 400mg/dL, whether albumin was ever > 3, any occurrence of unexpected bleeding and number of times it occurred, occurrence of any anaphylatic reaction, rate of blood stream infections as shown by positive blood cultures, rate of line infections and gram positive central venous catheter infections. Outcomes will be summarized for each study group based proportions, poisson rates, mean, minimum, or maximum over the subject follow-up period, and statistical significance of differences between groups will be estimated with exploratory purpopose via Fisher's exact test, Wilcoxon or t-tests, as appropriate.

We will also compare nutritional outcomes of the two groups including difference in weight-for- age Z-scores and height-for-age Z-scores from baseline to the moment in which the child starts enteral feeding and to the moment in which the child receives less than 10% of their calories from PN. Comparison between study groups will be performed via t-test or Wilcoxon tests, as appopriate. Using linear regression, we will explore adjustement for baseline alternative predictors of interest. Trends over time in Z-scores will also be explored using regression with repeatemd measure methods.

Analysis of Efficacy of Omegaven®

The primary outcome to gain preliminary evidence of efficacy will be based on the time from baseline to normalization of bilirubin level, i.e, first time point among three consecutive in which bilirubin is < 2 mg/dL. We do not anticipate that any subject will present a rebound on direct bilirubin after normalization. However, we will describe the cohort with respect to the frequency of rebounds in bilirubin levels.

Crude comparisons of time to normalize direct bilirubin levels between Omegaven® and soybean oil fat emulsion patients will be based on Kaplan-Meier curves and log-rank tests. We will estimate hazard ratios and adjust for potential baseline confounders using Cox-proportional hazard models. For all survival analysis based on non-parametric or semi-parametric methods, we will attribute an infinite time to event (i.e., time to event larger then the largest follow-up time in the whole study population) for subjects who die or receive a liver transplant before bilirubin is normalized. Subjects who die before their bilirubin levels normalize (particularly due to liver failure) have in fact the worse outcome (infinite time to normalize bilirubin) and were not censored before reaching the endpoint of interest. Results of these analysis will be compared with results of analysis excluding subjects who die or are transplanted. Time to reach a total bilirubin of 1.2 will also be compared using survival analysis methods. Analysis of this outcome will procede as described for direct bilirubin.

We will also describe individual profiles over time (i.e., 2 months before before baseline or birth until end of follow-up period) for all subjects using graphical methods. Trends in liver function markers over time will be explored using generalized linear models in which correlations of observations within subjects will be accounted using a generalized equations or random effects approach. In these models we will hypothesize that for both groups biochemical levels increase for all tests with equal slope before treatement. After treatment, however, levels should be decreasing for patients in the Omegaven® group. We will perform these analyses including only subjects who did not die or undergo transplantation and including all subjects but assigning for subjects who died or underwent a transplant their worse possible outcome after they died or had the transplant. Using descriptive statistics, we will also explore the association between spikes in blood tests over time and predictors including transfusions of red blood cell products and blood stream infections.

Assessment of efficacy will be also based on comparison of means (or medians) of the mean and maximum modified PELD scores of each subject across all follow-up weeks. Adjustments of these comparisons for potential confounders will be based on linear regression models. Mean rates of infection will be compared using logrank and Cox proportional hazards models. Proportions of liver transplant, mortality, and red blood cell product transfusion events between the two groups will be compared via Fisher's exact test (or Chi-square tests, when appropriate). Adjustments for potential confounders will be considered using exact stratified analysis and logistic regression models.

Missing Values

Since data will be prospectively collected in the Omegaven® group, we anticipate that data will be nearly complete, particularly for the safety outcomes. In both groups, we will explore imputing any laboratory values that are missing up to two visits in the middle of the follow-up period using linear or non-linear interpolation, as appropriate. To interpolate direct and total bilirubin, we will primarely use the two closest observations, since bilirubin could be very different in points in time located further apart from the missing observation. We will compare conclusions of analyses based on imputed values with analyses based on the available information.

Potential Study Limitations

The main limitation of our study results from the lack of comparability between the Omegaven® and historical control groups leading to potential confounding biases in our results. Two concerns could be: a) several health care standards and reporting systems changed (possibly improved) over the last 25 years (period in which controls were enrolled); and b) Omegaven® cases may be more severe, with more

advanced PNALD than historical controls, since they will be enrolled under a compassionate use protocol. Biases due to general improvement of health care outcomes could bias against controls the actual differences in safety (such as line infections) outcomes between Omegaven® (outcomes recorded now) and historical controls (outcomes recorded in the past). Conversely, improvement in reporting systems over time would tend to bias results in opposite direction, i.e., against Omegaven®. Since both biases may occur, we would expect that they would reduce or cancel each other. Also, we will compare all safety outcomes before and after treatment started in patients receiving Omegaven®, and compare conclusions of these analyses with analyses comparing Omegaven® with historical controls. Biases due to differential severity of omegaven and historical control patients is likely to occur but decrease the potential truth effect of Omegaven®.

Biases in our efficacy estimates could also result from misclassification, since our marker or reversal of cholestaisis, i.e., direct bilirubin does not accurately translate all components of liver function. Also, and more importantly biases could result from missing data, since more missing data is expected to occur in historical controls than in the Omegaven® cohort (differential pattern of missing). Misclassification due to lack of specificity or sensitivity of direct bilirubin as a marker of cholestasis would likely to be random, and thus lead to underestimation of the true effect of Omegaven® in reversal of cholestasis. Biases due to more outcomes missing in the control than in the Omegaven® group could lead to an overestimation of the effect of Omegaven®

d. Statistical Power and Sample Considerations

The number of subjects included in the Omegaven® group will be based on a compassionate use protocol and not on study power considerations. The number of subjects included in the soybean oil fat emulsion historical cohort group will not be based on study power considerations but rather on the number of eligible subjects from a pre-existing cohort.

The primary safety analysis will be descriptive and not based on statistical significance. However, in Table 4 we outline power to detect several differences in the frequency of adverse events, assuming 20, 25, or 30 patients, diverse proportion of subjects with adverse event in either treatment period and not with the adverse event in the other (proportion of discordant pairs), for a two-sided 5% significance level McNemar's tests. Table 5 includes estimates of power for a Fisher's exact test when comparing Omegaven® with historical control groups, assuming diverse frequency of occurrence of the adverse event in the control group, equal number of subjects in each group, and diverse differences in proportions between Omegaven® and soybean oil fat emulsion groups.

For lower proportions of discordant pairs, we would generally attain close to 80% power in McNemar's test. Even for higher proportions of discordant pairs, assuming the high differences between before and after treatment that we expect to observe, e.g., 50% or more, 80% power can be attained in McNemar's test (Table 4). In Fisher's exact test, we will attain 80% power or more to detect differences between Omegaven® and historical controls of 45% or larger, regardless of the frequency of adverse events in each group (Table 5).

Table 4 – Power to detect varying differences in proportions before and after treatment with Omegaven® in a McNemar's test. All calculations were based on an alpha significance level of 0.05.

Difference between proportions	Proportion of discordant pairs	McNemar's Test		
		Sample size in the Omegaven™ group		
		20	25	30
30%	40%	59%	72%	81%
	60%	44%	55%	63%
50%	60%	92%	97%	99%
	80%	79%	88%	93%
80%	85%	>99%	>99%	>99%
	95%	>99%	>99%	>99%

*Calculations performed Statxact.

Table 5 – Power to detect varying differences in proportions between Omegaven® and historical control groups in a Fisher's exact test. All calculations were based on an alpha significance level of 0.05.

Differences in the frequency of the event between Omegaven® and historical control groups	Frequency of the event in one of the comparison groups	Fisher's Exact Test		
		Sample size in each comparison group		
		20	25	30
35%	5%	72%	82%	89%
	25%	49%	65%	72%
	50%	57%	68%	78%
45%	5%	89%	95%	98%
	25%	73%	88%	92%
	50%	89%	95%	98%

*Calculations performed using N-query advisor.

e. Study Organization

Dr. Puder will serve as the principal investigator. Dr. Gura will serve as the managing co-investigator. Dr. Duggan, Dr. Raphael, Dr. Jaksic, Kathy Gura, and Alexis Potemkin will assist with patient enrollment. Drs. Puder, Gura, and Duggan along with the CRP staff will assist in study design and data analysis.Data collection will be done by the research nurses, with assistance from the nursing unit liasions, the study coordinator, and research assistants in Dr. Puder's lab. All individuals who assist in this function will have CITI training. The necessary CCI amendments and approvals will be obtained prior to any staff assisting in this function. The study coordinator will abstract the medical records and and complete the CRFs and a careful QC visual inspection of the CRFs prior to submiting them for data entry. The Research Coordinator will complete all data entry..

f. Data and Safety Monitoring Plan

Patients will be monitored while receiving Omegaven® treatment to observe for signs of Omegaven® toxicity. At the start of Omegaven® therapy, patients 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 demonstrated signs or symptoms of allergic reaction, the Omegaven® will be discontinued and the PI and attending physician will be notified. Selected safety labs will be evaluated by attending staff

and the Study Investigators for both clinical and research purposes. Blood samples will be taken prior to the start of therapy (baseline), and thereafter in accordance with the scheduled represented in the tables below.

Reversal/Safety Study Lab Schedule:

Patient Status	Parameter	Tests to be Performed	Frequency
Inpatient/receiving Omegaven®	Direct bilirubin >2 mg/dL	PN profile, AST, GGT, CRP, lipid Panel, PT, PTT, INR, fibrinogen, EFA Panel	Weekly
	Direct bilirubin ≤2 mg/dL	PN profile	Weekly
		PN profile, AST, GGT, CRP, PT, PTT, INR, fibrinogen, EFA panel, lipid panel	Monthly
Inpatient/off Omegaven®			
		PN profile, AST, GGT, CRP, lipid Panel, PT, PTT, INR, fibrinogen, EFA Panel	one complete set of post-Omegaven labs
Outpatient/on Omegaven®	Direct bilirubin ≥ 2 mg/dL	PN profile, AST, GGT, CRP, lipid Panel, PT, PTT, INR, fibrinogen, EFA Panel	Weekly
	Direct bilirubin ≤2mg/dL	PN profile, AST, GGT, CRP, lipid Panel, PT, PTT, INR, fibrinogen, EFA Panel	Monthly until off Omegaven and at least 1 direct serum bilirubin < 2 mg/dL

*minimum requirements, may be performed more frequently for routine clinical care

If under the discretion of the principal investigator the patient is able to return home and receive Omegaven®, the patient is required to return to Boston every 2 months or other mutually agreed upon schedule for evaluation and follow up. The Principle Investigator also requires for arrangements to be made through the patient's home health care agency for the required weekly or monthly blood draws the patient will need while at home in order to remain on Omegaven®. The lab results then must be faxed to Children's Hospital Boston in a timely manner. Additionally, measures will be taken to decrease the chance of administration errors when Omegaven® is given in the home. Families will be provided with a letter outlining strategies for reducing medication administration errors, such as independent double-checks. Also, families will be provided with fish stickers to be affixed to their Omegaven® pump to decrease the likelihood of using the incorrect pump to administer Omegaven®.

Dose reduction will occur if there is evidence of lipid intolerance (serum triglycerides > 200mg/dL) or evidence of bleeding. Growth indices include weight, length, and head circumference will also be monitored.

Other standard care laboratory results will be captured for the Omegaven® protocol. These are listed along with the standard schedule in Table 3.

The frequency of laboratory monitoring may be reduced to monthly or as clinically necessary, for patients who have been on a stable regimen of Omegaven® for a minimum of 4 months and whose serum bilirubin and hepatic enzymes have normalized.

The CAIR team completes rounds every Wednesday morning on all inpatient short bowel patients which incorporates all Omegaven® study patients. A complete comprehensive case review for all inpatients receiving Omegaven® therapy under the compassionate-use protocol and any outpatients issues are discussed among the CAIR team and with Dr. Puder, Dr. Gura, and the Omegaven® study nurses. All pertinent medical, nutritional, and psychosocial outpatient information is reviewed during these case reviews.

This study will be monitored by an independent data safety monitoring board (DSMB). The DSMB will have 6 members [(Dr. Robert Shamberger (Chair), Dr. Anne Hansen, Dr. John Watkin, Dr. Nicholas Tawa (BIDH), Senior level statistician TBD, and Judy Mahoney RN.] The DSMB will be chaired by a physician and surgeon who is not part of the Clinical Nutrition Service at Children's Hospital, Boston. The Board will also incude a CHB gastroenterologist and an external member from the Beth Isreal Deaconess Hospital. The Chair will receive copies of all adverse events reports and may call a DSMB meeting based on the reports received. The DSMB will meet formally every 6 months to review preliminary safety data. Prior to this, the Investigators had undergone periodic review by the CCI and met with the GCRC staff to discuss preliminary findings and address safety concerns, including infection rates and medication errors.

The responsibilities of this board will include:

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.

Review the research protocol, and amendments, informed consent documents, and plans for data and safety analysis.

Evaluate the progress of the intervention, including assessment of data quality and timeliness of data entry, participant recruitment, accrual and retention, and any other factors that may affect the study outcome.

Review any factors external to the study when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the trial.

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.

6. 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

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

Other expected adverse events that are common to all patients with short bowel syndrome, regardless of the type of fat emulsion they receive, include blood stream infections and re-admittance to hospital. Causes for re-hospitalization 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 >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 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.

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 and a single case of dramatic success. 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.

7. Potential Benefits

The potential benefits of this study 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 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. Phytosterol containing intravenous fat emulsions containing large quantities of omega 6 fatty acids have been associated with PN associated liver disease. 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.

.

8. Privacy Provisions

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.

9. Confidentiality Provisions

Loss of patient confidentiality is another risk in this study. The risk of loss of confidentiality will be reduced by the use of unique study ID numbers assigned to each participant. This number will appear in place of names on all study related documents and data forms. The study database will be password protected.

10. References

1. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery 1968;64:134-42.
2. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. Jama 1968;203:860-4.
3. Mullick FG, Moran CA, Ishak KG. Total parenteral nutrition: a histopathologic analysis of the liver changes in 20 children. Mod Pathol 1994;7:190-4.
4. Freund HR. Abnormalities of liver function and hepatic damage associated with total parenteral nutrition. Nutrition 1991;7:1-5; discussion 5-6.
5. Beath SV, Davies P, Papadopoulou A, Khan AR, Buick RG, Corkery JJ, Gornall P, Booth IW. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg 1996;31:604-6.
6. Greenberg GR, Wolman SL, Christofides ND, Bloom SR, Jeejeebhoy KN. Effect of total parenteral nutrition on gut hormone release in humans. Gastroenterology 1981;80:988-93.
7. Yeh SL, Chen WJ, Huang PC. Effects of L-glutamine on induced hepatosteatosis in rats receiving total parenteral nutrition. J Formos Med Assoc 1995;94:593-9.
8. Kubota A, Yonekura T, Hoki M, Oyanagi H, Kawahara H, Yagi M, Imura K, Iiboshi Y, Wasa K, Kamata S, Okada A. Total parenteral nutrition-associated intrahepatic cholestasis in infants: 25 years' experience. J Pediatr Surg 2000;35:1049-51.
9. Moss RL, Das JB, Ansari G, Raffensperger JG. Hepatobiliary dysfunction during total parenteral nutrition is caused by infusate, not the route of administration. J Pediatr Surg 1993;28:391-6; discussion 396-7.
10. Helms RA, Christensen ML, Mauer EC, Storm MC. Comparison of a pediatric versus standard amino acid formulation in preterm neonates requiring parenteral nutrition. J Pediatr 1987;110:466-70.
11. Moss RL, Haynes AL, Pastuszyn A, Glew RH. Methionine infusion reproduces liver injury of parenteral nutrition cholestasis. Pediatr Res 1999;45:664-8.
12. Meehan JJ, Georgeson KE. Prevention of liver failure in parenteral nutrition-dependent children with short bowel syndrome. J Pediatr Surg 1997;32:473-5.
13. Whalen GF, Shamberger RC, Perez-Atayde A, Folkman J. A proposed cause for the hepatic dysfunction associated with parenteral nutrition. J Pediatr Surg 1990;25:622-6.
14. Zamir O, Nussbaum MS, Bhadra S, Subbiah MT, Rafferty JF, Fischer JE. Effect of enteral feeding on hepatic steatosis induced by total parenteral nutrition. JPEN J Parenter Enteral Nutr 1994;18:20-5.
15. Kaminski DL, Adams A, Jellinek M. The effect of hyperalimentation on hepatic lipid content and lipogenic enzyme activity in rats and man. Surgery 1980;88:93-100.
16. Hultin M, Carneheim C, Rosenqvist K, Olivecrona T. Intravenous lipid emulsions: removal mechanisms as compared to chylomicrons. J Lipid Res 1995;36:2174-84.
17. Qi K, Al-Haideri M, Seo T, Carpentier YA, Deckelbaum RJ. Effects of particle size on blood clearance and tissue uptake of lipid emulsions with different triglyceride compositions. JPEN J Parenter Enteral Nutr 2003;27:58-64.
18. Nestel PJ. Effects of N-3 fatty acids on lipid metabolism. Annu Rev Nutr 1990;10:149-67.
19. Chen W. Effects of fat emulsions with different fatty acid composition on plasma and hepatic lipids in rats receiving total parenteral nutrition. Clinical Nutrition 1996;15:24.
20. Yeh S. Effects of fish oil and safflower oil emulsions on diet-induced hepatic steatosis in rats receiving total parenteral nutrition. Clinical Nutrition 1996;15:80.
21. Kinsella JE, Lokesh B, Broughton S, Whelan J. Dietary polyunsaturated fatty acids and eicosanoids: potential effects on the modulation of inflammatory and immune cells: an overview. Nutrition 1990;6:24-44; discussion 59-62.

22. Alwayn IPJ, Gura K, Nose V, Zausche B, Javid P, Garza J, Verbesey J, Voss S, Ollero M, Andersson C, Bistrian B, Folkman J, Puder M. Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. Pediatr Res. 2005 Mar;57(3):445-52. Epub 2005 Jan 19.
23.Van Aerde JE, Duerksen DR, Gramlich L, Meddings JB, Chan G, Thomson AB, Clandinin MT 1999 Intravenous fish oil emulsion attenuates total parenteral nutrition-induced cholestasis in newborn piglets. Pediatr Res 45:202-208.
24. Morlion BJ, Torwesten E, Lessire Al, et al. The effect of parenteral fish oil n leukocyte membrane fatty acid composition and leukotriene synthesizing capacity in postoperative trauma. Metabolism 1996; 45:1208-1213.
25. Grimminger F, Führer D, Papavassilis C, et al. Influence of intravenous n-3 liipid supplementation on fatty acid profiles and lipid mediator generation in patients with severe ulcerative colitis. Eur J Clin Invest 1993; 23:706-15.
26. Grimminger F, Mayser P, Papavassilis C, et al. A double blind randomized, placebo-controlled trial on n-3 fatty cid based lipid infusion in acute, extended guttate psoriasis. Rapid improvement of clinical manifestations and changes in neutrophil leukotriene profile. Clin Invest 1993; 7:634-43.
27. Mayeser P, Mrowietz U, Arenberger P, et al. ω-3 fatty acid based lipid emulsion in patients with chronic plaque psoriasis. J Am Acad Dermatol 1998; 38:539-47.
28. Heller AR, Fischer S, Rössel T, Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. Br J Nutr 2002; 87; Suppl 1:95-101.
29. Kolezko BV, Fürst P. Fish oil in parenteral nutrition in infants: clinical evidence and experience. Data on file, Fresenius- Kabi AG, Bad Homburg v.d.h.
30. Gura KM, Parsons SK, Bechard LJ, Henderson T, Dorsey M, Phipatanakul W, Duggan CP, Puder M Lenders C. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. Clinical Nutrition. 2005 Oct;24(5):839-47.
31. Andorsky DA, Lund DP, Lillehei CW, Jaksic T, DiCanzio J, Richardson D, Collier S, Lo C, Duggan C. Nutritional and other postoperative management of neonates with short-bowel syndrome correlates with clinical outcome. J Pediatr, 2001; 139:27-33.

11. Appendix Materials – please check off as appropriate if included with submission.

- ☐ Sponsor's Protocol
- ☐ Federal grant application (please submit 3 copies)
- ☐ Investigator brochure
- ☐ Survey, questionnaires, assessments
- ☐ Flow charts, schemas
- ☐ Recruitment letters, postings, flyers
- ☒ Other

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 2: Schedule for **Required** Safety Monitoring for Omegaven® Therapy

Lab Name	**Schedule***
Serum triglycerides	At baseline, weekly for 4 weeks, monthly thereafter
Coagulation labs	At baseline, weekly until direct bilirubin is < 2mg/dl, monthly thereafter
Fatty acid profile	At baseline, monthly thereafter

*minimum requirements, may be performed more frequently for routine clinical care

Table 3: **Suggested** Monitoring Schedule for Omegaven® Therapy

Parameter	Baseline (pre-Omegaven)	Daily	Q week* until direct bilirubin < 2mg/dL	Monthly* once direct bilirubin <2.0 mg/dL	Periodically*	Tube type volume
Weight	X	X				
Fluid balance	X	X				
Vital Signs	X	X				
Catheter site/function	X	X				
Laboratory test:						
Sodium	X		X	X		
Potassium	X		X	X		
Chloride	X		X	X		
Glucose	X		X	X		
BUN	X		X	X		
Creatinine	X		X	X		
Triglycerides	X		X	X		
Calcium	X		X	X		
Magnesium	X		X	X		
Phosphorus	X		X	X		
Prealbumin	X		X	X		
C reactive protein	X		X	X		
Albumin	X		X	X		
Total protein	X		X	X		
SGPT	X		X	X		
Alkaline phosphatase	X		X	X		
Bilirubin (total and direct)	X		X	X		
GGT	X		X	X		
AST	X		X	X		
Essential Fatty Acid Profile	X		X	X		2 mL red top
Free cholesterol	X		X	X		
Free fatty acids	X		X	X		
Lipid Panel	X		X	X		
Hemoglobin	X		X	X		0.6ml purple top
Hematocrit	X		X	X		
RBC	X		X	X		
WBC	X		X	X		
Platelets	X		X	X		
PT	X		X	X		1.5ml blue top
PTT	X		X	X		
INR	X		X	X		
Fibrinogen	X		X	X		
Selenium					X	Navy blue Metal free
Zinc					X	
Aluminum					X	
Copper					X	
Iron					X	
Carnitine					X	lithium heparin
Vitamins A,D,E					X	Call lab control
Retinol binding protein (check when getting Vit A)					X	3 ml red top

*More often as necessitated by clinical course; may be reduced in patients who are stable (i.e., home patients) and whose biochemical markers have improved.