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Protocol: COMPASSIONATE USE OF AN INTRAVENOUS FISH OIL LIPID EMULSION (OMEGAVEN®) FOR THE TREATMENT OF INTESTINAL FAILURE ASSOCIATED LIVER DISEASE IN CHILDREN (V3.0)

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Funding Source: Department of Surgery, Children's Hospital & Medical Center
Study Population: Patients with Parenteral Nutrition Associated Liver Disease (PNALD) requiring parenteral nutrition therapy at Children's Hospital & Medical Center.

ABSTRACT

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.

PURPOSE

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.

BACKGROUND
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.

Preliminary Studies/Progress Report
Animal Studies

In initial studies conducted at Children's Hospital Boston, it was 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, they 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 they 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.

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. Dr. Puder's 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 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 Dr. Puder's clinical trial at Boston Children's Hospital and 2 other unpublished clinical trials. These other 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.

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.

B. Patient Selection and Inclusion/Exclusion Criteria

After the diagnosis of PNALD is made, patients who are followed by the Department of Surgery, in conjunction with the patient's primary physician, will contact Dr. Jones and an evaluation will be performed. Cases may also include referrals of patients with PNALD from other healthcare facilities or self-referrals upon transfer to our institution. 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 solely 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 ≥ 2 mg/dl on at least the last two consecutive measures or by histology and/or currently on Omegaven through another protocol and unable to remain on that protocol due to transfer to our institution. Other causes of liver disease should be excluded. A liver biopsy is not necessary for treatment.
3. 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®).
4. Patients ages birth up to and including 18 years of age.

Exclusion Criteria:
1. Pregnancy
2. Other causes of chronic liver disease (Hepatitis C, Cystic fibrosis, 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; however, these patients will be excluded upon identification.

Screening Procedures
All patients receiving parenteral nutrition for short bowel disorders at CH&MC are followed by the Department of Surgery as primary or through consults. 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 performed as necessary. If the patient's status supports consideration of treatment, the option for experimental therapy will be investigated. A similar process will be utilized for self-referrals and potential patients referred from distant healthcare facilities and will be implemented once they have been transferred to our institution.

C. Description of Study Treatment
Bottles containing 50mL or 100 mL of 10% Omegaven® will be purchased from International

Pharmacy of Hamburg, Germany or directly from the manufacturer. FDA Approval is pending to allow for billing of Omegaven®. In the event that third party coverage is not available Children's Hospital & Medical Center will cover all Omegaven® 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. 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 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 entered in Epic and must contain the following data elements:

- Total daily dose to be 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.

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 Department of Surgery 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.

D. 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®. 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).

Outcome/Endpoints

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. Primary analyses for these and all other safety outcomes will be based on a follow-up time for Omegaven® 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.

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, maximum international normalized ratio (INR), and 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 evaluation of Omegaven® 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.

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.

E. Data Collection Methods, Assessments and Schedule
Data will be collected by the PI (BJ), the managing co-investigator (RC) and the clinical coordinator (MD). Hospital charts will be reviewed for pertinent clinical information. Results of liver biopsies and blood chemistries will be obtained from Epic within the computer system at Children's Hospital & Medical Center. 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.

F. Study Timeline
This study will end when the results of an FDA approved clinical trial proves Omegaven® treatment to be ineffective, the product is approved for use in the United States, or funding mechanism no longer exists to supply Omegaven® to study participants.

G. 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 UNMC Pediatric IRB 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 hemodynamic 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 UNMC Pediatric IRB 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 IRB and the FDA within 72 hours of the occurrence being known, or immediately if the event is fatal or life threatening as per UNMC Pediatric IRB 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 IRB's form for adverse/unexpected event reporting.

Adverse events are detected by Children's Hospital & Medical Center 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 Children's Hospital & Medical Center 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. Jones, Cusick) 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. 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 IRB with the adverse event form for review and 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 (i.e. Evidence of burr cell anemia (reported toxicity); Continued lipid intolerance (triglyceride >200) despite dose reduction attempts and administration modification; evidence of coagulopathy (INR> 2.0)).
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.

DATA STORAGE & CONFIDENTIALITY
This study is being conducted under an FDA Investigational New Drug Application. As such, FDA regulations must be followed. Personal Health Information (PHI) will be protected using standard policies and procedures developed through UNMC according to HIPAA guidelines. Subjects will be assigned specific reference numbers and maintained in a password protected database. The subject's name and medical record number along with the corresponding reference number will be stored in a separate access page. All the research data gathered and stored will be identified by reference number only. The research data will only be accessible to the investigators and data/administrative and healthcare personnel involved in the study. Consent forms and files will be stored in a locked office. Information will not be stored on any personal computer or laptop. The de-identified data will be used for research or regulatory purposes or to prepare research publications. The child's name will never appear in any reports or publications, or in any future disclosures. The child's PHI will be shared, as necessary, with the Institutional Review Board (IRB) and with any person or agency required by law. The research data is subject to disclosure for the duration of the research and until data analysis is complete.

Retention of Records
The study coordinator 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 and industry standards, the Primary Investigator will retain records for a period of no less than five (5) years following discontinuation of the study.

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.

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, variables will be transformed.

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

Analysis of Baseline Characteristics

For statistical purposes, baseline values will be defined as the last measurement before starting to administer Omegaven®. Descriptive statistics for all baseline relevant risk factors will be summarized using counts and percentages for categorical variables and means (and standard deviations) or medians (and interquartile ranges), when appropriate for continuous variables.

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. The period receiving Omegaven® will start 30 days after beginning PN with Omegaven® for the main analysis. Outcomes measured in the Omegaven® will be described for a period starting 30 days after baseline.

Primary outcomes measured 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 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.

We will also evaluate nutritional outcomes 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. Using linear regression, we will explore adjustment for baseline alternative predictors of interest. Trends over time in Z-scores will also be explored using regression with repeated 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.

Time to normalize direct bilirubin levels will be estimated using Kaplan-Meier curves. 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 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 worst outcome (infinite time to normalize bilirubin) and were not censored before reaching the endpoint of interest. Results of these analyses 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 estimated using survival analysis methods. Analyses of this outcome will proceed as described for direct bilirubin.

We will also describe individual profiles over time (i.e., 2 months 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. 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.

Missing Values
Since data will be prospectively collected, we anticipate that data will be nearly complete, particularly for the safety outcomes. 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 primarily 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.

Statistical Power and Sample Considerations
The number of subjects included in the study will be based on a compassionate use protocol and not on study power considerations. 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 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.

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).

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

Difference between proportions	Proportion of discordant pairs	McNemar's Test Sample Size		
		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%

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 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®	Direct bilirubin ≥ 2 mg/dL	PN profile	Weekly
	Direct bilirubin < 2 mg/dL	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

Safety Labs Schedule:

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

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 Children's Hospital & Medical Center 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 & Medical Center 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.

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 study team will round on all inpatients receiving Omegaven® therapy. A complete comprehensive case review for all inpatients receiving Omegaven® therapy under the compassionate-use protocol and any outpatients issues will be discussed among Dr. Jones, Dr. Cusick, and the study coordinator. All pertinent medical, nutritional, and psychosocial outpatient information will be reviewed during these case reviews.

This study will be monitored by an independent data safety monitoring board (DSMB). The DSMB will have 3 members [Dr. Shahab Abdessalam (Chair), Dr. Nicole Birge, and Dr. Gleb Haynatzki]. 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 after the first 4 enrolled subjects and then annually to review preliminary safety data.

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.

RISKS AND DISCOMFORT

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

Additional Risks
Risk of loss of privacy/confidentiality: There is a slight risk of loss of confidentiality, but this will be minimized as described in the Data Storage and Confidentiality section.

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. 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.

BENEFITS

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

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 potential complications of surgery or fulminant hepatic failure may be avoided.

PN associated liver disease is a life threatening condition. Available therapies (liver/small bowel transplant, intestinal lengthening, ursodiol, and 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. 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.

FINANCIAL CONSIDERATIONS

Although the FDA has approved charging 3rd party payers for the cost of the drug/shipping, few third party payers in the United States allow these charges currently. We do not intend to bill the patient's insurance carrier for the cost of the drug and related shipping charges.

CLINICALTRIALS.GOV (NCT#): 02328768

IND#: 125210

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APPENDIX

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 Bili < 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		
Bili (total and direct)	X		X	X		
GGT	X		X	X		
AST	X		X	X		
Ess. 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.