Use of Omega-3 Fat Emulsion (Omegaven) in Infants With Parenteral Nutrition Associated Liver Disease

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1.0 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 bilirubin, aminotransferase and alkaline phosphatase, and histologic alterations such as steatosis, steatohepatitis, lipidosis, cholestasis, fibrosis, and cirrhosis (3, 4). These abnormalities, which 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.

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

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.

2.0 Rationale and Specific Aims

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.

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.

Specific Aims /Objectives

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

Hypothesis for Aim 1:
1.1 – PN containing Omegaven™ will be safe for patients with respect to the risk of unexpected bleeding, coagulopathies, and other adverse events.
1.2 – PN containing Omegaven™ will promote more short-term growth and development than conventional fat emulsions.
1.3-Incidence of sepsis will be similar to historical incidence of sepsis on TPN and IL™

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 > 2.5 mg/dL, patients receiving Omegaven™ will reach a bilirubin level ≤ 2 mg/dL faster than patients receiving conventional fat emulsions. Additionally, patients receiving Omegaven™ will experience a decrease in their levels of bilirubin and other hepatic enzymes over time.
2.2 – Patients with surgical gastrointestinal disease and cholestasis will improve clinical hepatic status.
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.

3.0 Animal Studies and Previous Human Studies

Animal Studies

In initial studies at Children's Hospital Boston, they 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 their 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. They recognized that the model may not completely match the clinical, human, setting of intravenous PN-administration; however, their 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. 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. 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 at Children's Hospital Boston, 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™(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 (FDA IND #[redacted]). 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.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Patients aged 0 to 2 years 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 >2.5 mg/dl or more. Other causes of liver disease should be excluded. A liver biopsy is not necessary for treatment.
3. Signed patient informed consent.

4. 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. Other causes of chronic liver disease (Hepatitis C, Cystic fibrosis, biliary atresia, and alpha 1 anti-trypsin deficiency,)
2. Enrollment in any other clinical trial involving an investigational agent (unless approved by the designated physicians on the multidisciplinary team)
3.. The parent or guardian or child unwilling to provide consent or assent
4. Patients with severe hemorrhagic disorders
5. Patients with severe liver disease not caused by prolonged PN and renal insufficiency
6. Patients with uncontrolled diabetes mellitus

5.0 Enrollment/Randomization

NICU attendings will screen their patients for infants who need prolonged parenteral nutrition (TPN) and have Parenteral Nutrition Associated Liver Disease. The attending physician will ask the family if they would like more information about the study. Dr. Walsh will be notified of these infants, and assess if they are suitable candidates. Dr. Walsh or the NICU research nurses will explain the study to the infant's parents / legal guardians and obtain informed consent in the NICU at Vanderbilt Children's Hospital.

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.

6.0 Study Procedures

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 is pending from the FDA to allow for billing of Omegaven. Omegaven™ is manufactured by Fresenius Kabi AG, Bad Homburg v.d.h, Germany. Omegaven™ is formulated as an emulsion from fish oils. See attached Product Information Sheet.

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

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. 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 (Table 2 and 3), therapy with Omegaven™ will be initiated at the goal dose of 1 gram /kg/day and is infused over 12-24 hours. 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.

Table 2: Suggested Schedule Safety Monitoring for Omegaven™ Therapy

(To be done baseline pre-Omegaven™ therapy and weekly until direct bilirubin <0.4 mg/dL)

Parameter	Baseline	Biweekly	Monthly
Essential Fatty Acid Profile	X		X
PT	X	X	
PTT	X	X	
INR	X	X	

Table 3: Suggested Monitoring Schedule for Omegaven™ Therapy
(Amended December 26, 2006)

Parameter	Baseline (pre-Omegaven)	Daily	Q week*	Periodically**
Weight	X	X		
Fluid balance	X	X		
Vital Signs	X	X		
Catheter site/function	X	X		
Laboratory test:				
Sodium	X		X	
Potassium	X		X	
Chloride	X		X	
Glucose	X		X	
BUN	X		X	
Creatinine	X		X	
Triglycerides	X		X	
Calcium	X		X	
Magnesium	X		X	
Phosphorus	X		X	
Prealbumin	X		X	
C reactive protein	X		X	
Albumin	X		X	
Total protein	X		X	
SGPT	X		X	
Alkaline phosphatase	X		X	
Bilirubin (total and direct)	X		X	

GGT	X		X	
AST	X		X	
Copper				X
Iron				X
Vitamins A,D,E				X
Essential Fatty Acid Profile	X		X	
Free cholesterol	X		X	
Free fatty acids	X		X	
Lipid Panel	X		X	
Hemoglobin	X		X	
Hematocrit	X		X	
RBC	X		X	
WBC	X		X	
Platelets	X		X	
PT	X		X	
PTT	X		X	
INR	X		X	
Fibrinogen				
Selenium				X
Zinc				X
Carnitine				X
Aluminum				X
Retinol binding protein (check when getting Vit A)				X

* More often as necessitated by clinical course; may be reduced in patients who are stable and whose biochemical markers have improved. Refer to protocol for additional information

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.

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. 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 greater than 12 hours (use multiple syringes so as to keep maximum hang time of Omegaven™ source container less than 12 hours)

Discontinuation of Therapy

Patients will continue to be followed by the PI if in-patient or if discharged they will be followed in the Out-Patient GI Clinic upon discontinuation of therapy with Omegaven™ for a minimum of 2 months after the treatment is stopped.

Data Collection

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.

7.0 Risks

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

A recent review of the literature suggests a slight change in risk status. There was a single case report of an infant developing anemia : J Pediatr. 2010 Feb;156(2):324-6.e1, Parenteral fish oil-associated burr cell anemia. Mallah HS, Brown MR, Rossi TM, Block RC. The mechanisms responsible for formation of burr cells are unknown but have been attributed to changes in composition of the lipids of the red blood cell membrane. These
changes affect erythrocyte fragility and ultimately cause shape alterations, which make the red blood cells more susceptible to trapping and destruction by the spleen. None of the 13 infants in our study has developed any anemia and we will now monitor for that reported complication.

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.

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.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events (AEs) will be assessed and reported from the time of the first Omegaven™ infusion until exit from the study. In particular, the patient will be observed during and shortly after Omegaven™ administration for the occurrence of anaphylactic or allergic reactions. Other expected adverse events include death, blood stream infection; 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 VUMC 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 theVUMC IRB and the FDA within 72 hours of the occurance being known, or within 24 hours if the event is fatal or life threatening. This will be done in person, by telephone, or email, and by completion of the IRB form for adverse/unexpected event reporting.

Adverse events are detected by VCH Neonatology 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 VCH NICU staff are reported to the Principal Investigator immediately by telephone or pager, and subsequently to the appropriate board or committee.

The PI, Dr. Walsh, will be responsible for assuring that adverse event reporting requirements are actually met. 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

9.0 Study Withdrawal/Discontinuation

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.

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.

10.0 Statistical Considerations

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.

Primary outcomes measured in the Omegaven™ group will include routine measurement of the direct bilirubin levels and whether the INR was ever > 2.
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..

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 using Omegaven™ 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. Liver transplant, mortality, and red blood cell product transfusion events will be collected.

Limitation of Study

Biases in our efficacy estimates could also result from misclassification, since the marker of reversal of cholestaisis, i.e., direct bilirubin does not accurately translate all components of liver function.

11.0 Privacy/Confidentiality Issues

Study data will be collected on paper Case Report Forms (CRF's) developed by the PI. The CRF can only be accessed by valid investigators in the study. Study participants are only identified in the CRF with a sequentially generated study number. A paper Log with the identifiers of the study subjects will be kept in a locked research office and only available for view to the PI, Sub-Investigators, the safety monitor if requested and the FDA if requested.

Infants and children enrolled will be assigned a study number that will identify the patient on Case Report Forms. Study numbers will be assigned sequentially with enrollment. Only the investigators involved with the study will have access to the log revealing which patients were assigned which study

numbers. No identifiable information (such as patient name, medical record number) is included in the CRF.

12.0 Follow-up and Record Retention

The original copy of the electronic CRF will remain on server for six years after the conclusion of the trial, and then destroyed.