Protocol Title: Compassionate Use of Omegaven® in the Treatment of Parenteral Nutrition Induced Hepatic Injury

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Study Product:	Omegaven®
IND Number:	110,979

Confidentiality Statement

Protocol Synopsis

PRINCIPAL-INVESTIGATORS: Pankaj Vashi, MD, Cancer Treatment Centers of America & Carolyn Lammersfeld, RD, Cancer Treatment Centers of America

TITLE OF THE STUDY: Compassionate Use of Omegaven® in the Treatment of Parenteral Nutrition Induced Hepatic Injury

STUDY MEDICATION: Omegaven®

INDICATION: Parenteral Nutrition (PN) Induced Hepatic Injury

STUDY PHASE: Compassionate Use

STUDY CENTER: Cancer Treatment Centers of America (CTCA), Zion, Illinois

NUMBER OF PATIENTS: Approximately 30 patients will be included, with potential of including up to 50 patients depending on preliminary data

STUDY PURPOSE OBJECTIVES:

Primary: To examine whether Omegaven, an omega-3 based lipid emulsion, can improve or prevent further deterioration of PN-induced hepatic dysfunction

Secondary: To examine the effects of Omegaven, an omega-3 based lipid emulsion, on immune function and markers of the inflammatory process

STUDY DESIGN:

Patients who have been receiving treatment at CTCA and have been receiving outpatient PN and develop PN-induced hepatic injury, or will be starting home PN and have existing hepatic dysfunction.

Patients will receive their initial infusion of PN containing Omegaven at a CTCA location to observe for adverse reactions. Omegaven will be given on Day 1 at a dose of 0.1 g/kg body weight (1 mL/kg). On Day 2 or 3, it will be increased to 0.2 g/kg body weight (2 mL/kg). The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr).

After tolerance is established, patients will have the option to receive treatment at home through Coram for 4 weeks or until hepatic dysfunction is reversed (established normalization of liver function tests/serum bilirubin < 2).

INCLUSION CRITERIA:

A patient must meet the following criteria to participate in this study:

I.1 Male or Female; ages 18 to 80
I.2 Receiving treatment at CTCA
I.3 Receiving PN (either in the infusion center or at home)
I.4 Have existing hepatic dysfunction defined as Elevation of >3x the normal level of one or more of the following: Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), or Alanine Aminotransferase (ALT) and/or Bilirubin > 2 mg/dl in the absence of biliary obstruction.
I.5 Able to provide informed written consent (patient or legally acceptable representative)

EXCLUSION CRITERIA:

Patients will be excluded from participating in the study for the following reasons:

E.1 Hypertriglyceridemia (fasting triglycerides [TG] > 400)
E.2 Allergy to fish or egg protein
E.3 Currently on therapeutic doses of Coumadin, heparin, or low molecular weight heparin.
E.4 Hemodynamically unstable
E.5 Bilirubin > 5 mg/dL
E.6 Documented progression of liver metastases
E.7 Unstable diabetes with known diabetic ketoacidosis within 7 days of screening
E.8 Recent cardiac infarction taking plavix
E.9 Severe hemorrhagic disorders

E.10 Embolism
E.11 Sepsis
E.12 Undefined coma status
E.13 Renal insufficiency with calculated creatinine clearance < 30 mL/min.
E.14 Pregnancy or lactation

TREATMENT:

Treatment with Omegaven will be given on study Day 1 at a dose of 0.1 g/kg body weight (1 mL/kg). On Day 2 or 3, it will be increased to 0.2 g/kg body weight (2 mL/kg). The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr).

Omegaven will be co-infused via y-site. Containers will be changed every 12 hours. Omegaven will be given through a 1.2 micron inline filter.

Omegaven will be given daily for:

- Up to 4 weeks, or
- Until normalization of alkaline phosphatase, AST, & ALT

The patient may receive other lipids to meet essential fatty acid (EFA) and/or additional calorie needs.

EFFICACY OUTCOME VARIABLES:

- Maximum conjugated bilirubin
- Time to resolution of bilirubin or death
- Average improvement in bilirubin, alkaline phosphatase, AST, & ALT

SAFETY OUTCOME VARIABLES:

- Summary of laboratory results
- Summary of AEs for each patient

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CO_2	Carbon Dioxide
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTCA	Cancer Treatment Centers of America
DCF	Data Clarification Form
DHA	Docasahexaenoic Acid
DMC	Data Monitoring Committee
EFA	Essential Fatty Acid
EPA	Eicosapentaenoic Acid
G	gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
Hbg	Hemoglobin
Hct	Hematocrit
Hr	hour
ICF	Informed Consent Form
ICU	Intensive Care Unit
INR	International Normalized Ratio
IRB	Institutional Review Board
Kg	kilogram
LDH	Lactic Acid Dehydrogenase
LOS	Length of Stay
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligram per deciliter
mL	Milliliter
ml/kg	Milliliters per kilogram
MPV	Mean Platelet Volume
NCR	No Carbon Required
PN	Parenteral Nutrition
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Count
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
TG	Triglycerides
TNF	Tumor Necrosis Factor
WBC	White Blood Count
WHODDE	World Health Organization medical dictionary
<	Less than
>	Greater than
=	Equal to

2. INTRODUCTION

2.1. Background

Parenteral nutrition (PN), when required for long-term nutrition support, may lead to hepatic dysfunction (ADA pocket guide to PN). PN can be the cause of hyperbilirubinemia and elevated liver function tests. Patients at increased risk of developing hepatic dysfunction from PN are those with primary gastrointestinal disorder, pre-existing liver disease, malnutrition, or sepsis (ref). The cause of this dysfunction may be related to the provision of excess calories, excess individual macronutrients, and deficiencies of choline, L-carnitine, and/or glutamine. This dysfunction can progress to liver failure in patients requiring long-term PN.

There are recommendations to try to prevent PN induced hepatic dysfunction. They include but are not limited to avoiding excess calorie, carbohydrate, and/or lipid infusion; limiting infusion time; some oral or enteral nutrients if possible; and possibly adding choline, L-carnitine, and/or glutamine to the PN. Despite following these recommendations, patients may still develop PN induced hepatic dysfunction. This may result in the need to discontinue PN.

Patients with advanced cancer requiring PN for long-term nutrition support may be at increased risk for developing this condition due to gastrointestinal failure, liver metastases, and malnutrition. If these individuals begin to experience elevation of bilirubin and/or liver function tests, the calories from macronutrients may have to be reduced, resulting in underfeeding in those that may already be malnourished. If after reducing calories from macronutrients and adding L-carnitine to the PN, liver function does not improve, the PN may have to be held or discontinued. This results in severe under nutrition or in some cases no source of nutrition.

Lipid emulsions are added to parenteral nutrition to provide calories and essential fatty acids. Currently, the lipid emulsions used in the United States (U.S.) are long chain triglycerides from soybean or safflower oil, which have a high ratio of n-6 to n-3 polyunsaturated fatty acids (Wanten 2007). There is some evidence to suggest that the n-6 lipid emulsions used in PN may be associated with PN induced steatohepatitis and an increase in pro-inflammatory eicosanoids resulting in immune suppression (Wanten 2007, Kinsella 1990). Omega-3 fatty acid containing lipid emulsions are not available in the U.S., but they are available and are being studied in Europe and Taiwan. Omega-3 fatty acid containing lipid emulsions have been shown to prevent or attenuate PN-induced hepatosteatosis in normal rats and mice (Chen 1996, Alwayn 2005). In addition, these solutions have been shown to ameloriate diet-induced hepatosteatosis in rats (Yeh 1996). Most recently, in a non-randomized study using historical controls, 18 infants with short-bowel syndrome who developed cholestasis, were given a fish-oil based fat emulsion. Reversal of cholestasis was achieved 4.8 times faster (9.4 weeks vs. 44.1 weeks) in those receiving the fish oil emulsion compared to historical controls that received soybean emulsions. Also, the fish-oil based emulsion was safe and was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, or infection (Biank 2008).

In addition to the potential role omega-3 lipid emulsions may play in reversing PN induced hepatic injury, they may help decrease the inflammatory response and have a beneficial effect on clinical outcomes. Morlion et al. (1996) found that 5-days of a parenteral fish oil supplement resulted in a change in leukotriene synthesis to a more favorable 5 series and a decreased length of stay in surgical patients. Pluess et al. (2007) demonstrated that a two day infusion of a fish-oil emulsion (Omegaven) in healthy volunteers given an endotoxin increased eicosapentaenoic acid (EPA) and docasahexaenoic acid

(DHA) content in platelet phospholipids and decreased tumor necrosis factor alpha compared to controls.

Other studies have found a decrease in intensive care unit (ICU) days and length of stay with fish-oil emulsions. Heller et al. (2006) in a prospective, open label, multiple-center trial found that administration of a fish-oil emulsion reduced mortality, antibiotic use, and length of stay in different diseases. A total of 661 patients receiving PN for ≥ 3 days were included in the study to evaluate dose-dependent effects of fish-oil emulsion. The mean dose given was 0.11 g/kg/day. The most favorable effects on survival, infections, and length of stay were at doses of 0.1 and 0.2 g/kg/day. Antibiotic use was lowered by 26% with doses of 0.15-0.2 g/kg/day. Finally, a dose of 0.23 g/kg/day was associated with a decrease in ICU LOS. No bleeding or other adverse events were reported.

Heller et al. (2004) also found that fish oil supplemented PN improved liver and pancreas function in a prospective, randomized, double-blind clinical trial on 44 patients having major abdominal cancer surgery. Patients were randomized to receive either PN with soybean oil or a combination of soybean and fish oil for 5 days. The fish oil group had reduced AST, ALT, & bilirubin after surgery. The fish oil group also trended towards having a shorter ICU stay. Also, the soybean only group lost 1.1±2.2 kg, while the fish oil group did not lose weight.

In a prospective, double-blind, randomized, controlled study of 42 patients requiring radical resection for colon cancer, Liang et al. (2008) found a favorable effect on the inflammatory and immune response with the use of an omega-3 lipid emulsion postoperatively. All patients received PN for 7 days postoperative. The control group received standard omega-6 lipid emulsion while the study group had some of the omega-6 lipid in their PN replaced with omega-3. On post-op day 8, serum IL-6 levels were significantly lower with omega-3. Also, with omega-3, the ratio of CD4+/CD8+ was significantly increased; TNF-α was decreased; and CD4+ lymphocyte percentage was increased.

2.2. Risk Category

(45 CFR 46.405) Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual patients.

2.3. Rationale

Omegaven may be effective in stabilizing or reversing hepatic injury associated with the use of PN. In addition, omega-3 lipid emulsions may help decrease the inflammatory response and have a beneficial effect on clinical outcomes. This compassionate use protocol provides a mechanism for physicians to better understand the efficacy of Omegaven for the treatment of patients with advanced cancer requiring PN for long-term nutrition support who have developed PN-induced hepatic injury or who have existing hepatic dysfunction.

2.4. Statement

This study will be conducted in compliance with the protocol, the guidelines of Good Clinical Practices (GCP), the current revision of the Declaration of Helsinki, and the applicable regulatory requirements.

3. OBJECTIVES

The primary objective for this study is to examine if an omega-3 based lipid emulsion (Omegaven) can improve or prevent further deterioration of PN induced hepatic dysfunction.

The secondary objective for this study is to examine the effect of an omega-3 based lipid emulsion (Omegaven) on immune function and markers of the inflammatory process.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This compassionate use study will include patients with advanced cancer requiring PN for long-term nutrition support who have developed PN-induced hepatic injury or who have existing hepatic dysfunction. Therapy with Omegaven will be provided at an initial dose of 0.1 g/kg body weight (1ml/kg) and increased to 0.2 g/kg body weight (2ml/kg) on day 2 or 3 of treatment. For patients > 120% ideal body weight, adjusted body weight will be used. The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr). Omegaven will be co-administered via a y-site infusion, with containers being changed every 12 hours. The patient may receive other lipids to meet Essential Fatty Acid (EFA) and/or additional calorie needs. Patients will receive the initial infusion of PN containing Omegaven at Midwestern Regional Medical Center (MRMC) in the infusion center to observe for adverse reactions. If an adverse reaction is observed, IV steroids & benadryl will be administered & Omegaven will be discontinued. Patients will continue to receive infusions at CTCA for the first 2 to 3 days of dosing. After tolerance is established, patients will receive treatment at home with Coram. All study patients will have a Screening Visit; Day 1, Day 2 and Day 3 visits; and weekly visits for one month (see Table 2).

Table 2: Study Schedule

Visit:	Screening	Day 1	Day 2	Day 3	Weekly Visits	Final Study Visit/ Early Withdrawal
Informed Consent Form	X					
Inclusion/Exclusion Criteria	X					
Physical Exam	X					X
Vital Signs	X	X	X	X	X	X
Medical History	X					
Blood hematology/chemistry	X	X	X	X	X	X
Triglyceride level monitoring[1]		X	X	X	X	
Dispense study medication		X	X	X	X	
Infusion given at MRMC[2]		X	X			
Infusion given at MRMC or at the patient's home				X	X	
Adverse Events (AEs)		X	X	X	X	X
Concomitant medications		X	X	X	X	X
Education on home PN & Omegaven		X				
Assess patient compliance				X	X	
Clinical supplies accounted for & destroyed						X

[1] Triglyceride level monitoring will occur daily from the time the patient begins Omegaven dosing until Omegaven dosing is complete.

[2] Infusions will be given at MRMC for 2-5 days, after which the infusions can be moved to the patient's home.

4.2. Study Procedures by Visit

4.2.1. Screening Visit

Cancer patients with hepatic injury will be offered Omegaven for compassionate use situations when there are no satisfactory alternative treatments. Patients meeting the criteria for this study will be screened for participation at the MRMC. The following will occur for all patients at the Screening Visit:

- Prior to performing any study procedures, the patient will be informed about the trial and asked to sign and date the Informed Consent Form (ICF). The person who conducted the informed consent discussion will also be required to sign and date the ICF.
- Patient eligibility will be assessed based on the inclusion and exclusion criteria (Sections 5.1 and 5.2).
- A complete physical examination with vital signs and medical history and historical medications will be done.
- Blood will be drawn for hematology and chemistry lab panels (see Section 4.3.1).

4.2.2. Day 1 Visit

The Day 1 Visit and the Screening Visit can occur on the same day. The Day 1 Visit will occur at CTCA, and the following will occur at this visit:

- Blood will be drawn for hematology and chemistry lab panels (see Section 4.3.1).
- Any medication changes and/or medications taken since the Screening Visit will be recorded.
- Education will be provided by site personnel on Omegaven and on home PN for those patients who will be receiving infusions in their homes.

Patients will be treated with an initial dose of Omegaven at 0.1 g/kg body weight (1ml/kg) by continuous infusion at CTCA. The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr). Triglycerides (TGs) will be monitored daily and a dose reduction will occur if:

  - TG levels rise above 400 mg/dL,
  - If evidence of bleeding occurs.
- Any changes to the patient's health (Adverse Events/AEs) from the time infusion begins will be recorded.

4.2.3. Day 2 Visit

The Day 2/Day 3 Visit will occur at CTCA. At this visit, the following will occur for all patients:

- Vital signs will be taken.
- Blood will be drawn for hematology and chemistry lab panels (see Section 4.3.1).
- Omegaven dosing will occur via continuous infusion at CTCA. The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr).
- The Omegaven dose will be increased to 0.2 g/kg body weight (2 ml/kg).
- AEs and Concomitant Medications since the previous visit will be recorded.

4.2.4. Day 3 Visit

The Day 3 Visit may occur at the patient's home. At the Day 3 Visit, the following will occur for all patients:

- Vital signs will be taken.
- Blood will be drawn for hematology and chemistry lab panels (see Section 4.3.1).
- Omegaven dosing will occur via continuous infusion at either CTCA or in the patient's home. The Omegaven dose will remain at 0.2 g/kg body weight (2 ml/kg). The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr).

- AEs and Concomitant Medications since the previous visit will be recorded.
- Drug accountability will be performed by the homecare nurse to assess patient compliance if the patient has received doses in the home without a nurse present.

4.2.5. Weekly Visits During Home Use of Omegaven (up to 4 weeks of treatment)

Patients will be monitored by healthcare nurses during home health visits every week until withdrawal from the study. The first weekly visit will occur 7 ±1 days after the first dose, and continue every 7 ± 1 days thereafter. During these home health visits the following will occur:

- Vital signs will be taken.
- Blood will be drawn for hematology and chemistry lab panels (see Section 4.3.1).
- Omegaven dosing will occur via continuous infusion at either CTCA or in the patient's home. The Omegaven dose will remain at 0.2 g/kg body weight (2 ml/kg). The infusion rate will not exceed 0.5mL Omegaven/kg body weight/hr (corresponding to 0.05g fish oil/kg/hr).
- AEs and Concomitant Medications since the previous visit will be recorded.
- Drug accountability will be performed by the homecare nurse to assess patient compliance if the patient has received doses in the home without a nurse present.

Omegaven will be given for:

- 4 weeks, or
- Until serum bilirubin is < 2 mg/dL, or
- Until normalization in liver function tests.

4.2.6. Final Study Visit/Early Withdrawal Visit

At the patient's Final Study Visit/Early Withdrawal Visit, the following will occur:

- A physical exam will be performed.
- Vital signs will be taken.
- Blood will be drawn for hematology and chemistry lab panels and additional toxicity labs (see Section 4.3.1).
- AEs and Concomitant Medications since the previous visit will be recorded.
- Drug accountability will be performed by the homecare nurse to assess patient compliance if the patient has received doses in the home without a nurse present.
- Any remaining clinical supplies will be accounted for and destroyed.

4.3. Description of Study-Specific Procedures

4.3.1. Diagnostic Tests

The following diagnostic laboratory tests will be performed:

- **Blood Hematology and Chemistry**
  - Hematology: white blood cell count (WBC or leukocyte count), WBC differential count, red blood cell count (RBC or erythrocyte count), hematocrit (Hct), hemoglobin (Hbg), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, and mean platelet volume (MPV)

- Chemistry: Blood Urea Nitrogen (BUN), carbon dioxide (CO_2), creatinine, glucose, serum chloride, serum potassium, serum sodium, serum calcium, serum phosphorus, serum magnesium, triglycerides and a liver panel: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, total protein, direct bilirubin (conjugated), total bilirubin
- Additional Labs: An additional clot tube of blood will be collected and stored at baseline and at the end of 4 weeks or withdrawal from study to evaluate treatment response.

The investigator, or a qualified designee who is part of the study team, will promptly review each lab report as it becomes available. If the investigator deems a value outside the reference range to be "clinically significant," then she/he will record it as an adverse event (AE). Lab reports will become a part of the source documentation.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

A patient must meet the following criteria to be included in this study:

I.1 Male of Female; ages 18 to 80
I.2 Receiving treatment at CTCA
I.3 Receiving PN (either in the infusion center or at home)
I.4 Have existing hepatic dysfunction defined as Elevation of >3x the normal level of one or more of the following: Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), or Alanine Aminotransferase (ALT) and/or Bilirubin > 2 mg/dl in the absence of biliary obstruction.
I.5 Able to provide informed written consent (patient or legally acceptable representative)

5.2. Patient Exclusion Criteria

A patient will be excluded from the study for any of the following reasons:

E.1 Hypertriglyceridemia (fasting triglycerides [TG] > 400)
E.2 Allergy to fish or egg protein
E.3 Currently on therapeutic doses of Coumadin, heparin, or low molecular weight heparin.
E.4 Hemodynamically unstable
E.5 Bilirubin > 5 mg/dL
E.6 Documented progression of liver metastases
E.7 Unstable diabetes with known diabetic ketoacidosis within 7 days of screening
E.8 Recent cardiac infarction taking plavix
E.9 Severe hemorrhagic disorders
E.10 Embolism
E.11 Sepsis
E.12 Undefined coma status
E.13 Renal insufficiency defined as creatinine clearance < 30 mL/min.
E.14 Pregnancy or lactation

5.3. Patient Withdrawal Criteria

Patients may be terminated from the study for the following events and reasons:

W.1 The patient chooses to withdraw for any reason
W.2 The Investigator chooses to terminate the patient from the study. Reasons could include:

a. Occurrence of AEs related to the use of Omegaven; adverse reaction to Omegaven
b. Patient non-compliance
c. Patient discovered after enrollment not to have met the protocol entrance criteria

W.3 Therapy goals are reached: patient able to meet and sustain nutrient needs by oral nutrition
W.4 Patient lost to follow-up
W.5 The principal-investigator terminates the study
W.6 If bilirubin elevates to > 5 mg/dl due to obstruction
W.7 Requires open surgical procedure
W.8 Documented progression of liver metastases contributing to worsening of hepatic dysfunction.

If a patient does not return for a scheduled visit every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. Patients will only be considered lost to follow-up if study personnel are unable to communicate with the patient or the patient‘s legally acceptable representative by three telephone attempts and certified letter. Reasons for withdrawal will be specified in the patient’s study file, and will include date of discontinuation of investigational product and date of study withdrawal.

6. CONCOMITANT MEDICATIONS/TREATMENT

The patient will be queried regarding concomitant use of medications at all study visits. All concomitant medication use (both prescription and over-the-counter, including herbal medications and nutritional supplements) will be reported during the study, and recorded in the patient’s study file.

Patient will be instructed to avoid any oral supplements containing omega-3 fatty acid supplements during this protocol.

The patient may receive other lipids to meet essential fatty acid (EFA) and/or additional calorie needs.

7. COMPLIANCE

Treatment compliance can be assessed using drug accountability records. The home healthcare nurse will collect any used/unused bottles at each visit and maintain a patient accountability record of all study medication that is distributed, administered, and collected for destruction.

8. INVESTIGATIONAL MATERIALS AND MANAGEMENT

8.1. Investigational Product

8.1.1. General Investigational Product Information

Bottles containing 50 mL or 100 mL of 10% Omegaven will be purchased from International Pharmacy of Hamburg, Germany. Omegaven is manufactured by Fresenius Kabi AG, Bad Homburg v.d.h, Germany. Omegaven is formulated as an emulsion from fish oils.

8.1.2. Dosing

Patients will be treated with Omegaven on day 1 at a dose of 0.1 g/kg body weight (1 ml/kg). On day 2 or 3, it will be increased to 0.2 g/kg body weight (2 ml/kg). For patients > 120% ideal body weight, adjusted body weight will be used for dosing. The infusion rate will not exceed 0.5 ml Omegaven/kg body weight/hr = 0.05 g fish oil/kg body weight/hr.

Omegaven will be co-infused via a y-site. Containers will be changed every 12 hours. Omegaven will be given through a 1.2 micron inline filter.

Omegaven will be given for:

- 4 weeks, or
- Until serum bilirubin is < 2 mg/dL, or
- Until normalization of liver function tests.

8.1.3. Dispensation

Omegaven will be dispensed by the CTCA pharmacy and homecare pharmacies per the applicable policies and procedures for fat emulsions.

8.1.4. Storage and Handling

Omegaven bottles will be stored at room temperature at ≤ 25° C (do not freeze). Damaged or suspect drug will be returned unused to Fresenius-Kabi. Containers should be shaken before use.

8.1.5. Accountability

All supplies for the study will be accompanied by accountability and shipping documents and will be maintained by the CTCA pharmacy and/or the homecare pharmacy. 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.

8.1.6. Dose Adjustments

A dose reduction will occur if:

- TG levels rise above 400 mg/dL,
- If evidence of bleeding occurs.

9. ASSESSMENT OF EFFICACY AND SAFETY

9.1. Outcome Variables

Efficacy and safety will be assessed using the following outcome variables:

- Laboratory results
- AEs reported by the patient and/or identified by study personnel
- Resolution of hepatic injury

9.2. Adverse Event (AE) Recording/Reporting

An AE is any untoward medical occurrence in a patient or clinical investigation patient participating in a clinical study and which does not necessarily have to have a causal relationship with this treatment or

clinical study. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include illnesses, signs, or symptoms, independent of causality, that appear or worsen during the course of the study. Whenever the investigator is confident of the diagnosis, he/she should group together as a single illness all related signs, symptoms, and abnormal laboratory test results (e.g., cough, rhinitis, and sneezing should ordinarily be reported as "upper respiratory tract infection").

An investigator will promptly review each lab report. Laboratory AEs are defined as clinical laboratory results that are outside of the normal ranges and are deemed clinically significant by the investigator. Clinically significant laboratory results will be recorded as AEs. Laboratory reports will become a part of the patient's study file.

Procedures, such as surgery, should not be reported as AEs or Serious Adverse Events (SAEs). However, the medical condition for which the procedure was performed should be reported if it meets the AE/SAE definition. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted in comments. In addition, an elective surgery (and any related hospitalization) whether or not there is an existing medical condition should not be reported as an AE.

The AE reporting period for this study begins at the time the first Omegaven infusion is administered and ends at the final study visit. Any abnormal physical examination findings identified during screening will generally be considered part of the medical history and not an AE. A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the medical history/physical) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

All AEs will be recorded in each patient's study file. The following definitions will be applied to AE reports:

Severity

MILD	Awareness of signs or symptoms, but they are easily tolerated
MODERATE	Enough discomfort to cause interference with usual activity
SEVERE	Incapacitating, with inability to work or do usual activity

Action Taken

NONE
TREATMENT OTHER THAN MEDICATIONS REQUIRED
MEDICATIONS REQUIRED
DISCONTINUED (Study medication permanently stopped)

Relationship to Study Medication

NONE	Causal relationship can be ruled out
POSSIBLY	Causal relationship at least reasonably possible, i.e., relationship can't be ruled out
DEFINITELY	Causal relationship is certain

Patients experiencing AEs that result in study drug discontinuation or those experiencing AEs that are present at the end of their participation in the study will receive follow-up until the AE is resolved, attributed to a cause other than study medication administration, or assessed as chronic or stable.

9.3. Serious Adverse Event (SAE) Recording/Reporting

An SAE for this study is one that meets any one of the following criteria:

- Fatal or life-threatening
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability/incapacity
- Important medical event

Medical and scientific judgment should be exercised in deciding whether an important medical event is serious. Although the event may not be immediately life threatening, fatal, or result in hospitalization, it should be considered serious when it jeopardizes the patient, or requires an intervention to prevent a serious outcome as defined above. Examples of serious medically important events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsion that do not result in hospitalization.

The term “life threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. The term “in-patient hospitalization” in the definition of “serious” refers to an event in which the patient was admitted to the hospital for one or more days, even if release on the same day; or an emergency room visit, which results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes criteria (e.g., important medical event).

The SAE reporting period begins at the time the first Omegaven infusion is administered and ends at the last study visit. SAEs that are considered at least possibly related to the study medication or that occur in a pregnancy that began while the patient was using the study medication can be reported at any time.

All SAEs will be followed through resolution or until the investigator attributes the SAEs to a cause other than the study medication or assesses them as chronic or stable. Follow-up SAE reports should adhere to the same procedures and timelines as initial reports. In addition, any SAE that occurs subsequent to the reporting period that the investigator assesses as possibly related to the study medication should also be considered for follow-up.

9.4. IND Safety Reporting

The Principal-Investigator for this IND shall promptly review all information relevant to the safety of the drug obtained or otherwise received from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the Principal-Investigator. The Principal-Investigator of a clinical study of a marketed drug is not required to make a safety report for any AE associated with use of the drug that is not from the clinical study itself.

9.4.1. Written IND Safety Report

The Principal-Investigator shall notify FDA and all participating investigators in a written IND safety report of:

- Any AE associated with the use of the drug that is both serious and unexpected; or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Each notification shall be made as soon as possible and in no event later than 15 calendar days after the Principal-Investigator's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format. In each written IND safety report, the Principal-Investigator shall identify all safety reports previously filed with the IND concerning a similar AE, and shall analyze the significance of the AE in light of the previous, similar reports.

Follow-up information to an IND Safety Report shall be submitted as soon as the relevant information is available. If the results of the Principal-Investigator's follow-up investigation show that an AE that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; Principal-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made. Additional safety information shall be submitted, as appropriate, in an information amendment or annual report.

9.4.2. Telephone or Fax IND Safety Reports

The sponsor shall also notify FDA by telephone or by fax of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the Principal-Investigator's initial receipt of the information.

9.5. IRB Safety Reporting

Adverse event submissions to the Institutional Review Board (IRB) responsible for this study will follow the responsible IRB's requirements.

10. DATA MANAGEMENT

10.1. Data Management

All patient study files will be centralized with the Principal-Investigator.

10.2. Sample Size Determination

This is a compassionate use study that is expected to enroll 30 patients.

10.3. Disposition and Baseline Assessment

In the event that a patient withdraws prematurely from the study, the reasons for withdrawal will be documented in the patient's study file. Patients who discontinue study medication or withdraw prematurely from the study will be summarized, together with the reason(s) for discontinuation.

10.4. Outcomes Analysis

This is a compassionate use study, with no comparator; therefore the endpoints will be descriptively summarized (continuous data will be presented as mean, standard deviation, median, minimum and maximum; categorical data will be presented as number and percentage). All patients who receive any amount of study medication will be analyzed. The outcome evaluations will include:

- **Laboratory results** – Laboratory values will be summarized at baseline and as change from baseline to worst follow-up values.
- **AEs reported by the patient and/or identified by study personnel** – AEs may be categorized into common terms and summarized as incidence and event rates. If there is sufficient data the incidence rates may also be summarized by AE severity and relationship to study medication.
- **Resolution of hepatic injury** – Resolution of hepatic injury will be summarized as incidence and if there is sufficient data may also be presented as time to resolution.
- **Days of PN** – Days of PN will be summarized.

10.5. Data Monitoring Committee

No plans for a Data Monitoring Committee (DMC).

10.6. Study Termination

This is a compassionate use study, intended to make a study medication available to patients who would otherwise not be able to receive this medication, therefore there is no predefined completion of this study. When the study is terminated for any reason, the patients will be treated as deemed appropriate by their usual healthcare provider. Some of the possible reasons for study termination are patient safety, Principal-Investigator termination of the study, etc.

Safety will be monitored throughout the study and if a safety concern indicative of a risk for the individual patients or the study population is identified at any time during the study, this will warrant further review and may result in the termination of the study.

10.7. Study Medication Administration

Study medication administration will be summarized. Any deviation from the planned dosing schedule will be documented and summarized.

10.8. Concomitant Medications

Concomitant medications are the medications that are taken during the study. Information on the concomitant medications will be collected in the patient's study file.

11. STUDY ADMINISTRATION

11.1. Adherence to the Protocol

Except for changes that are intended to eliminate an immediate hazard to patients, the approved protocol shall be conducted as described. Any protocol deviation or violation must be documented. Any protocol-related issue that poses an immediate or significant hazard to patients must be reported to the IRB immediately.

The Principal-Investigator may not implement any deviation or change to the protocol without prior review/favorable opinion of the appropriate regulatory authorities (e.g., IRB), except where necessary to eliminate an immediate hazard to a patient or when the change involves only a logistical or administrative aspect of the study (e.g., change of telephone numbers, ancillary personnel). Any deviation from the protocol must be documented and explained in written communication to the appropriate regulatory authorities.

This clinical study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), and the applicable regulatory requirements. Where applicable, the protocol designates study responsibilities to the "Investigator". Those tasks may be performed by the Principal Investigator or qualified designee.

11.2. Amending the Protocol

Any change to the protocol, once the final version has been issued, has to be detailed in a protocol amendment. All protocol modifications and amendments must be prepared for and approved by the IRB. All amendments must be numbered, dated and signed. Amendments cannot be implemented until final approval from the IRB.

11.3. Direct Access to Source Data/Documents

All representatives of the Principal-Investigator with direct access to patients' medical records will take reasonable precautions within the constraints of applicable regulatory requirements to maintain the confidentiality of the patients' identity. Auditors of the IRB and government inspectors may evaluate the study and must be allowed access to the patient study files, source documents and other study files. Audit reports will be kept confidential.

11.4. Quality Control and Quality Assurance

Quality assurance measurements are designed to ensure that complete, timely and accurate data are submitted, that protocol requirements are followed, and that complications and/or AEs are immediately identified. Quality assurance audits may be carried out during the conduct of the study. Quality assurance personnel independent of personnel conducting the study will carry out these audits. The quality assurance auditor should have access to all medical records, the Principal-Investigator's study-related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

11.5. Data Monitoring Committee (DMC)

No plans for a DMC.

11.6. Ethical Considerations and Patient's Consent

11.6.1. Ethical Considerations

The study will be carried out in accordance with the principles stated in the Declaration of Helsinki and in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

11.6.2. Institutional Review Board (IRB)

According to the applicable regulatory requirements, the investigator will submit the study documentation to the relevant IRBs. The letter of approval from the IRB (or a copy), which contains a list of the names and occupations of the members of the IRB having participated at the session, as well as a list of submitted documents, must be received by the Principal-Investigator prior to study medication being received at the study site. Patients must not be entered into the study until approval of the IRB(s) as defined by local regulatory requirements. All subsequent substantial amendments must be submitted to the IRB(s) for approval/information.

11.6.3. Written Informed Consent

A patient may be included in this study only after an IRB-approved Informed Consent Form (ICF) has been signed and dated by the patient. The patient must be informed about the content of the planned

study as well as on the benefit/risk ratio. The person who conducts the informed consent discussion at the study site will also be required to sign and date the ICF.

11.7. Data Handling and Recordkeeping

11.7.1. Patient Study File Completion

All patient study files will be filled out in permanent ink or typed. Corrections of data on the patient study files will be made only by crossing out the incorrect data and writing the correct values next to those crossed out. Each correction will be initialed and dated by the person making the correction. If corrections are made after review and signature by the Investigator, the Investigator will be made aware of the changes and his/her awareness will be documented by initialing and dating the changes.

11.7.2. Retention of Records

The site shall retain study medication disposition records, patient study files, and source documents for all patients enrolled for the period required by applicable regulatory requirements, the Institution in which the study will be conducted, or for a minimum of two years after shipment and delivery of the study medication is discontinued. The site should take measures to prevent accidental or premature destruction of the study documents for as long as they have to be maintained.

11.8. Regulatory Documentation

Documentation responsibilities of the site before or during the study include the following:

- Maintain accreditation or certification number and a list of reference ranges from any local laboratory that will be used (if applicable).
- Maintain appropriate regulatory forms along with a current copy of a curriculum vitae and medical license for each investigator in the study.
- Maintain a list of all persons whose participation materially affects the study (ancillary personnel). Must also include their training and/or title and the role they will assume in the study. If any changes to study personnel are made during the study, the log outlining the delegation of authority will be updated.

11.9. Final Study Report

A final study report will be prepared by the investigator according to applicable regulatory guidance.

11.10. Financing and Insurance

The study is fully financed by the Sponsor (Coram) and is insured.

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