CONFIDENTIAL

Clinical Study Protocol

(IND 104,748)

Title of Study:

Prospective Evaluation of a Parenteral Omega-3 Fatty Acid Preparation (Omegaven™) in Therapy of Patients with TPN-Induced Cholestasis

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Principal Investigator:

David F Mercer, MD, PhD
Director, Intestinal Rehabilitation Program
Assistant Professor of Surgery
University of Nebraska Medical Center
983285 Nebraska Medical Center
Omaha, NE 68198-3285
Telephone: 402-559- 6955
Fax: 402-559-3434

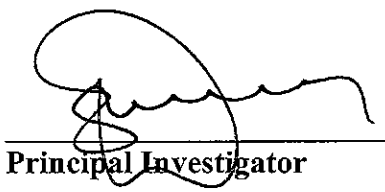
Research Facility:

Intestinal Rehabilitation Program
University of Nebraska Medical Center
983285 Nebraska Medical Center
Omaha, NE 68198-3285
Telephone: 402-559-2556
Fax: 402-559-3434

Drug Supplier:

Pharmacy International
Adenauerallee 1
20097 Hamburg, Germany
E-mail: mail@pharmacy-international.de
Telephone: +49 40 41 45 59 61
Fax: +49 40 2802518

In signing this protocol, I agree to conduct this study in accordance with this protocol. I further agree to comply with other pertinent regulatory requirements as set forth in 21 CFR Part 312.



Principal Investigator **Date** 3/5/9

TABLE OF CONTENTS

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, and children requiring prolonged courses of PN are at risk for developing PN-associated liver disease. Animal studies have shown that IV fat emulsions 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. We hypothesize that a fat emulsion comprised of omega-3 fatty acids (i.e., fish oil) such as Omegaven™ will be well tolerated and will reduce the inflammatory effect in the liver of prolonged PN exposure, with the potential of reversing 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 PN until they are able to ingest adequate nutrition enterally.

All patients in the Intestinal Rehabilitation Program at UNMC with an abnormal serum bilirubin (>2mg/dL), receiving PN and not meeting an exclusion criteria will be approached for enrollment. Upon enrollment, the PN lipid source will be switched to Omegaven, and patients will continue to be followed in standard fashion for ongoing intestinal rehabilitation. Patients will continue to have regular follow-up including laboratory evaluation at least once weekly, with periodic radiologic and endoscopic evaluation as per our standard of care. As hypertriglyceridemia is a possible side effect of Omegaven, weekly triglyceride levels will be added to regular labs. Patients will be continued on Omegaven until weaned from intravenous lipds per standard of care. Clinical data will be collected prospectively and will be compared with historical controls.

BACKGROUND AND RATIONALE

Patients with intestinal failure are unable to support growth or maintain health without some provision of nutrition parenterally. The Intestinal Rehabilitation Program at the University of Nebraska Medical Center is a multidisciplinary team focused on achieving enteral nutritional independence through optimization of intestinal function and autologous reconstruction of the GI tract. The program functions, along with small bowel transplantation, as part of the comprehensive intestinal failure program at UNMC. Many of our patients have excellent bowel rehabilitation potential given sufficient time for recontruction and intestinal adaptation, but are limited by concurrent progression of parenteral nutrition-associated liver disease (PNALD). The ability to slow or reverse PNALD may dramatically impact on our ability to treat intestinal failure.

Lipids are necessary in PN dependent patients due to their high caloric value and essential fatty acid content. In the United States, most patients dependent upon PN receive parenteral fat emulsions composed of soybean oils, which have been implicated in predisposing patients to PN-associated liver disease (PNALD). There is evidence in the scientific literature supporting use of lipid formulations comprised mainly of omega-3 fatty acids to halt or reverse the progression of PNALD (Gura, 2008; Diamond, 2009). It is believed that fish oil-based formulations such as Omegaven™ mediate reduction of liver injuiry through inhibition of de novo lipogenesis, reduction of arachidonic acid-derived inflammatory mediators, 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, educe impairment of bile flow which is seen in cholestasis caused by conventional fat emulsions (Alwayn, 2005; Van Aerde, 1999). By administering Omegaven™ in place of conventional soybean fat emulsions we hope to reverse or prevent the progression of PNALD, allowing sufficient time for intestinal rehabilitation and eventual cessation of parenteral nutrition.

We propose to conduct a prospective evaluation of the use of Omegaven™ for the provision of parenteral lipid calories in concert with an active ongoing program of inestinal rehabilitation. Our main outcome of interest will be need for small bowel transplantation, with secondary outcomes including improvement in clinical measures associated with PNALD and need for liver transplantation. This study will be conducted in both pediatric and adult intestinal rehabilitation patients.

STUDY PROTOCOL

Hypothesis

Established parenteral nutrition (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.

Objectives

The primary objective of this study is to evaluate the need for small bowel transplantation. Clinical data will be collected prospectively and will be compared with historical controls.

Secondary objectives are to determine if there are improvements in clinical measures associated with established parenteral nutrition- associated liver disease (PNALD).

Efficacy and Safety Variables

The efficacy and safety variables in this study will be the change from the baseline assessment to the end of follow-up assessment or end of treatment assessment for the variables listed below. The variables will be determined from: the measurement of body weight, the recording of TPN prescriptions, blood and urine analyses, radiology reports, GI exams, and possible liver biopsies.

- Parenteral Nutrient Requirements (determined from the TPN/PN prescription)
  - TPN/PN infusions (days/week)
  - TPN/PN fluid volume (cc/week)
  - TPN calories (kcal/week)
  - TPN protein (g/week)
  - TPN lipid (g/week)
  - Intravenous vitamins (type and # of infusions/week)
  - Intravenous trace elements (type and # of infusions/week)

- Assessment of Nutritional Status
  - Body Composition
    - Body Weight
  - Nutrient and Metabolic Profile (Blood analyses)
    - Vitamins- A, B12, C, D, E, folate
    - Minerals and trace elements - calcium, phosphorus, iron, selenium, zinc
    - Serum Proteins - total protein, albumin, globulin
    - Lipid profile - essential fatty acids levels
    - Citrulline, D-lactic acid
    - Serum Electrolytes – (sodium, potassium, chloride, bicarbonate, magnesium)

- Assessment of Hydration Status/ Renal Function (Blood analyses)
  - Blood urea nitrogen
  - Serum creatinine

- Assessment of Liver Function (Blood analyses)
  Total bilirubin, direct and indirect bilirubin, alkaline phosphatase, SGOT, SGPT, LDH.

- Assessment of Upper and Lower GI tract/Liver
  Upper and Lower endoscopy, mucosal biopsies and bacterial cultures
  Ultrasound of abdomen/Small bowel follow through, Barium enema
  Liver biopsy (based on clinical indication)

Study Design

This study will be a prospective, non-randomized, open-label study of Omegaven™ with a total enrollment of 100 patients, for provision of parenteral lipid calories. The study cohort, receiving the PN at 1g/kg/day, will be compared to historical controls at UNMC where parenteral lipid calories were provided exclusively through soybean-based formulations, as well as, assessing the study cohorts need for small bowel and liver transplantation.

A. Basic Design Characteristics
The study will include 4 periods, as described below.

1. Screening
Prior to the Evaluation Period, appropriate documentation will be obtained to determine which patients may qualify for the study.

2. Evaluation
During this period, the Investigator will evaluate to confirm eligibility. All these procedures are performed at initial evaluation on all patients in the Intestinal Rehabilitation Program, regardless of entry into a study. In addition to a review of body systems, the baseline evaluations will include the recording of body weight and routine urine and blood laboratory analyses. These blood and urine analyses will determine vitamin, trace element, essential fatty acid levels, serum electrolytes, hydration status, kidney function and liver function. Patients will also have radiology and GI exams. It is possible the evaluation may include a liver biopsy. The patient's pre-study TPN prescription will also be recorded.

3. Treatment
The Treatment Period will not begin until the patient undergoes a full initial evaluation. Informed consent will be obtained before treatment is initiated. After the initial evaluation is complete and inclusion criteria are found to be met, therapy with Omegaven™ will be initiated at the goal dose of 1 gram per kilogram per day, 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 central route. The same standards of care provided to all patients receiving parenteral nutrition solution will be followed, with routine nutritional monitoring.

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™ or resume therapy with the conventional fat

emulsions so that additional parenteral fat calories can be given. The clinical team will determine if the patient should be removed from the protocol, and the IRB and FDA will be notified.

Orders for Omegaven™ will contain the following data elements;

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

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

4. Treatment/Follow-up Period

During the follow-up period, patients will continue to be followed by the Intestinal Rehabilitation Program per our standard care for any patient on PN: All patients in IRP are followed with regular blood work, including CBC/diff and CMP at least weekly initially, and in most cases 2-3 times per week. Based on clinical progress, the frequency of laboratory evaluation may be reduced, but is rarely less than once weekly until patients are stable and off PN. These procedures and tests would continue to be performed.

In addition to standard nutritional monitoring, essential fatty acids and serum triglycerides levels will be sent monthly. If a patient should experience lipid intolerance, then serum lipid profiles, including triglycerides, will be sent weekly for the first 4 weeks of therapy, and if stable will be reduced to every two weeks. This monitoring is additional to what would be standard in this population. Any adverse experiences will be recorded for every patient throughout the entire enrollment of the study.

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

Upon returning home, patients will be returned to the care of the physician who referred them for participation in the study. Arrangements will be made with the patient's primary care physician to continue usual follow-up. Patients will initially be seen by their primary care physician within one week of returning home.

Measurements and Evaluations

The following assessments will be performed at Evaluation, during the Treatment and Treatment/Follow-up Periods

<u>Evaluation Assessments</u>

- <u>Parenteral Nutrient Requirements (determined from the TPN/PN prescription)</u>
  - TPN/PN infusions (days/week)
  - TPN/PN fluid volume (cc/week)
  - TPN calories (kcal/week)
  - TPN protein (g/week)
  - TPN lipid (g/week)
  - Intravenous vitamins (type and # of infusions/week)
  - Intravenous trace elements (type and # of infusions/week)

- Assessment of Nutritional Status
  - Body Composition
  - Body Weight

  Nutrient and Metabolic Profile (Blood analyses)
  Vitamins- A, B12, C, D, E, folate
  Minerals and trace elements - calcium, phosphorus, iron, selenium, zinc
  Serum Proteins - total protein, albumin, globulin
  Lipid profile - essential fatty acids levels
  Citrulline, D-lactic acid
  Serum Electrolytes – (sodium, potassium, chloride, bicarbonate, magnesium)

- Assessment of Hydration Status/ Renal Function (Blood analyses)
  Blood urea nitrogen
  Serum creatinine

- Assessment of Liver Function (Blood analyses)
  Total bilirubin, direct and indirect bilirubin, alkaline phosphatase, SGOT, SGPT, LDH.

- Assessment of Upper and Lower GI tract/Liver
  Upper and Lower endoscopy, mucosal biopsies and bacterial cultures
  Ultrasound of abdomen/Small bowel follow through, Barium enema
  Liver biopsy (based on clinical indication)

- Vital Signs
- Baseline Signs and Symptoms
- Physical Examination
- Total 24-hour oral/enteral intake
- Total 24-hour urine and stool volumes

Treatment Period

- Vital Signs (daily)
- Signs and Symptoms, daily
- Daily TPN/PN intake
- Total 24-hour oral/enteral intake
- Total 24-hour urine and stool volumes

- Clinical Chemistries - (to include any or all or the following at the discretion of the investigator, 1 or more times per week based on the clinical status of the patient):
  Blood urea nitrogen (BUN)
  Creatinine
  Electrolytes (sodium, potassium, chloride, bicarbonate, magnesium)
  Calcium
  Phosphorus
  Serum amylase
  Total Protein
  Albumin
  Triglycerides
  Liver function (total bilirubin, direct and indirect bilirubin, alkaline phosphatase, SGOT, SGPT, LDH)

Extended Outpatient Treatment Period (PN Treatment Outpatient)

- Weight (daily)
- Daily TPN/PN intake
- Clinical Chemistries - (to include any or all or the following at the discretion of the investigator, once per week:
  Blood urea nitrogen (BUN)
  Creatinine
  Electrolytes (sodium, potassium, chloride, bicarbonate, magnesium)
  Calcium
  Phosphorus
  Serum amylase
  Total Protein
  Albumin
  Triglycerides
  Liver function (total bilirubin, direct and indirect bilirubin, alkaline phosphatase, SGOT, SGPT, LDH)

Treatment/Follow-up Assessments

- Parenteral Nutrient Requirements (same as the Evaluation Period)
- Assessment of Nutritional Status (same as the Evaluation Period)
- Assessment of Hydration Status/ Renal Function (same as the Evaluation Period)
- Assessment of Liver Function (same as the Evaluation Period)
- Parenteral Nutrient Requirements (same as the Evaluation Period)
- Signs and Symptoms

Inclusion Criteria

The first 100 eligible patients must meet the conditions listed below:

- Patients must be enrolled in the Intestinal Rehabilitation Program at the University of Nebraska Medical Center, and:
- Be unable to meet nutritional needs solely by enteral nutrition and be expected to require PN for at least another 30 days
- Have clinical evidence of parenteral nutrition associated liver disease (PNALD) as defined as direct bilirubin of 2mg/dl or more. A liver biopsy is not necessary for treatment.
- Signed patient informed consent.

Exclusion Criteria

To be eligible for entry into the study, patients must not have any of the conditions listed below:

- Be pregnant or lactating
- Allergies or clinical conditions precluding safe use of Omegaven™
- Parent or guardian or child unwilling to provide consent or assent
- Inability or unwillingness on the part of the parent/guardian or child to follow clinical recommendations of the Intestinal Rehabilitation Program

Omegaven™ Dosages
Pharmacy-International will be the Drug Supplier for this study. The Omegaven™ will be delivered to the study site, where it will be stored in the hospital pharmacy, at the appropriate temperature and prepared for infusion.

Dosing Instructions and Schedule
During the treatment period, patients will receive an approximate daily infusion of Omegaven™ at a dose of 1g/kg/day, to be infused over 12-24 hours.

Omegaven™
The dose of Omegaven™ (1g/kg/d) will be administered by the nursing staff when the patient is in the hospital and administered by the patient (adult) or parent, if patient is a child, when the patient is outpatient during treatment.

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™ or resume therapy with conventional fat emulsions so that additional parenteral fat calories can be given.

Monitoring and Possible Dose Reductions
In addition to standard nutritional monitoring, essential fatty acids will be sent monthly and serum triglyceride levels will be sent weekly. 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 will 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 will 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 and 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 is listed for a liver or liver/intestinal transplant and an organ becomes available, the participation in this protocol will not preclude them from receiving the transplant.

Disruption of Therapy
In the event that treatment with 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)

Treatment will be discontinued and not restarted if the patient experiences a significant allergic reaction. Omegaven™ should not be administered to patients allergic to fish or egg protein.

Discontinuation of Therapy

Patients will continue to be followed by the UNMC Intestinal Rehabilitation Program upon discontinuation of therapy with Omegaven™ until they are completely free of any rehabilitation needs and are tolerating a full diet by mouth.

Side Effects (that may lead to Disruption or Discontinuation of Omegaven™):

The infusion of Omegaven™ can lead to prolonged bleeding time and an inhibited platelet aggregation. The administration of Omegaven™ should be stopped or reduced if there is a marked increase in blood glucose levels during infusion. Undesirable effects that are seen during 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, Dyspnea, Flushing or cyanosis, Lack of Appetite, nausea, vomiting, Headache, pain in 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.

Contraindications to Omegaven™ include the following:

Impaired lipid metabolism, Severe hemorrhagic disorders, Unstable diabetes mellitus, Collapse and shock, Stroke/embolism, Recent cardiac infarction, and Undefined coma status

Storage and Handling of Omegaven™

All Omegaven™ received and dispensed by the Investigator or his designee will be inventoried and properly accounted for throughout the study. The Omegaven™ will be stored in a refrigerated, secured area, with controlled access until administration. The patient will be instructed to store the Omegaven™ in a similar fashion once they leave the in-house setting and are discharged home.

Patient Discontinuation

The Investigators may discontinue an individual patient from the study at any time. They may voluntarily withdraw at any time. A patient may experience Dose Modification, Disruption of Therapy, or Discontinuation of Therapy from the study for the following medical or administrative reasons.

Dose Modification for Lipid Intolerance -

- If lipid intolerance develops, defined as serum triglyceride levels > 200 mg/dL, all sources of lipid intolerance should be considered and addressed (drugs, renal disease, etc). If the triglycerides continue to remain high despite the aforementioned interventions, a dosage reduction of the current dose will be considered.

Disruption of Therapy -

- In the 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.

Discontinuation of Therapy –

- 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.

- Adverse Event (AE) – Any patient with anaphylactic or allergic reactions to Omegaven™ will not continue treatment and will be withdrawn from the protocol.

- Inter-current Illness – If a patient develops an illness during the course of the study that is not associated with the condition under study and that requires treatment inconsistent with the protocol requirements (such as an interruption of regular participation in the study), the patient may be discontinued from further participation in the study. A patient may also be discontinued from the study if he develops an inter-current illness or complication that in any way justifies his withdrawal from the study. However, if an inter-current illness develops which can be managed without significant interference with the requirements of the protocol, the patient need not be discontinued.

- The patient will complete treatment with Omegaven™ in this study when he/she is completely off PN, develops a contraindication for further use, or the patient/family requests to be removed from the study.

Statistical Analysis

Data from the two sets of patient population will be pooled and compared (i.e., current protocol patients prescribed Omegaven™ PN compared to historical controls where parenteral lipid calories were provided exclusively through soybean-based formulations). Potential for effect in different patient populations will be minimized by matching patients enrolled in the Omegaven™ protocol to historical controls. Frequency matching will be utilized given the difficulty of paired matching in this patient population. Specific matching criteria will include gender, age, etiology of short bowel syndrome, and severity of liver disease (parenteral nutrition- associated liver disease).

Continuous data will be expressed as mean +/- SEM. A two-way repeated measure ANOVA will be used to compare differences in the two groups with respect to changes between the Evaluation assessment and the subsequent analyses performed at Treatment and Treatment/Follow-up Assessments. Incidence of adverse events in each treatment arm will be compared using Fisher's exact test. Univariate and multivariate analysis will be used to identify baseline factors that may influence outcome. A P-value <0.05 will be considered statistically significant.

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