Clinical Study Report Synopsis

in accordance with section 13 GCP-V

Version 01, 02.11.2022

Study title: Intravenous Fish Oil based Lipid Emulsion as Pharmaconutrient Strategy in High-Risk Cardiac Surgery Patients: a Phase II Dosing Study

Sponsor's Protocol Code Number: 16-118

EudraCT Number: 2016-003902-14

National Competent Authority reference: 4041928

Initial National Authority Approval: 07.06.2017

Name of Sponsor:

RWTH Aachen, represented by the principal, represented by the Dean of the Medical Faculty,

Univ. - Prof. Dr. rer. nat. Stefan Uhlig

Pauwelsstraße 30, 52074 Aachen

Tel.: 0241 / 80 80092, Fax. 0241 / 80 3390092

Email: ctc-a-spoqs@ukaachen.de

Name of Finished Product(s):

Omegaven

Name of Active Substance(s):

Eicosapentanoic acid / Docosahexaenoic acid (Fish oil)

Study Title:

Intravenous Fish Oil based Lipid Emulsion as Pharmaconutrient Strategy in High-Risk Cardiac Surgery Patients: a Phase II Dosing Study

Study design: multi-center, randomized-controlled, three-arm, parallel-group phase II dose-finding study

Final Protocol version: Version 05 dated 2017-07-28

Amendments: Protocol Amendment 01

Amendment Identification	Reason(s) for changes	Date of approval by the National Authorities
Substantial Amendment 01	Amendment of protocol	24.08.2017

Final Patient Informed Consent version: Version 03 dated 2017-05-18

Investigator(s):

Prof. Dr. med. Christian Stoppe

Site(s):

Department of Intensive Care Medicine, University Hospital RWTH Aachen
Pauwelsstraße 30, 52074 Aachen

Publication (reference): none

Study period: not applicable, as no sites were initiated or subjects enrolled

Date of first subject enrolment: not applicable, as no sites were initiated or subjects enrolled

Date of last subject completed: not applicable, as no sites were initiated or subjects enrolled

Early Termination: 11.10.2022

Due to administrative problems on the sponsor's side, start of recruitment was not feasible for a long period. The resulting increase in financial and regulatory requirements led to the decision to terminate the trial early.

Phase of Development: II

Objectives and criteria for evaluation:

Objective(s): In this dose-finding study we aim to determine the safety and efficacy / optimal tolerable dose of FO administered intravenously as Omegaven® in high-risk cardiac surgery patients, recruitment of trial patients, adherence to protocol and contamination with other FO products.

Primary endpoints:

- safety and efficacy
- feasibility

Secondary endpoints:

- Anti-inflammatory response
- Oxidative stress
- Inflammatory response on the immune system
- Effect on body's immune competence
- Immune phenotype and activation of immune cells
- Safety parameters in blood
- Pharmacokinetic profile
- Change in SOFA score
- ICU length of stay
- Hospital length of stay
- Length of ventilation
- Number of infection
- Persistent Organ Dysfunction+death (POD+death)
- 30-day mortality

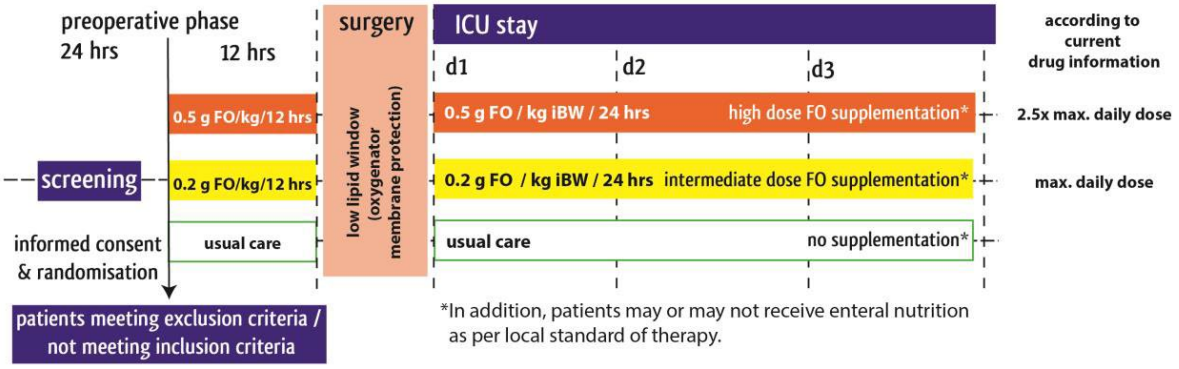
- Hospital mortality rate
- Quality of Life after 3 and 6 month
- Membrane incorporation of PUFAs in immune cells
- activation of protective survival kinases such as ERK1/2 and Akt
- adverse and serious adverse events

Methodology:

Patients meeting the inclusion criteria will be randomly assigned to one of the following treatment groups:

- Group 1: Patients will receive standard nutrition therapy (including enteral and parenteral feeding) in accordance to local standards, no study medication. Pre-operative treatment will be conducted in accordance to local standards and will be comparable to group 2 and 3.
- Group 2: Patients will receive 0.20 g/kg IBW FO based lipid emulsions and standard nutrition therapy (including enteral and parenteral feeding). See study schedule for administration schedule.
- Group 3: Patients will receive 0.50 g/kg IBW FO based lipid emulsions and standard nutrition therapy (including enteral and parenteral feeding). See study schedule for administration schedule.

Study intervention scheme



Number of subjects:

Planned: 144

Analysed: 0

After approval of the trial, the trial site was not initiated and no trial participants have been recruited or enrolled in the trial.

Diagnosis and main criteria for inclusion and exclusion:

Study population: 144 adult (≥ 18 years) male or female patients undergoing cardiac surgery (including women of child-bearing potential using contraception)

Inclusion criteria:

1. Age ≥ 18 years scheduled to undergo elective cardiac surgery with the use of CPB and cardioplegic arrest that exhibit a high perioperative risk profile as defined by the presence of one or more of the following:
   I. Included patients should exhibit a significantly increased perioperative risk profile defined as a predictive operative mortality EuroSCORE 5% or by complex/combined surgical procedures.
   II. Planned valve surgery combined with CABG or multiple valve replacement/repair surgeries or combined cardiac surgical procedures involving the thoracic aorta.
2. Written informed consent prior to study participation

Exclusion criteria:

1. Known hypersensitivity to fish oil/ fish products or egg protein
2. Emergency open heart surgery
3. Severe dyslipidemia (triglycerides > 400 mg/dl)
4. Severe renal or hepatic insufficiency (Patients with Cirrhosis Child's Class C Liver Disease)
5. Pregnancy or lactation period
6. Inability or unwillingness of individual to give written informed consent
7. Not study related fish oil supplementation
8. Not expected to survive an additional 48 hours from screening evaluation
9. Lack of commitment to full, aggressive care (anticipated withholding or withdrawing treatments in the first week but isolated DNR acceptable)
10. Patients admitted with Diabetic Ketoacidosis or non-ketotic hyperosmolar coma
11. Patients receiving and extracorporeal mechanical assist device (e.g. ECLS, or IABP) or for advanced heart failure therapies (e.g. TAH, VAD)
12. Enrolment in an industry sponsored randomized trial within the last 30 days (co-enrolment in academic randomized trials will be considered on a case by case basis)

Test product(s):

Name of finished product(s): Omegaven

Marketing authorization number(s): 34164.00.00

Name of active substance(s): Eicosapentanoic acid / Docosahexaenoic acid (Fish oil)

Dose(s):

- Group 2: 0.20 g/kg IBW FO based lipid emulsions
- Group 3: 0.50 g/kg IBW FO based lipid emulsions

Mode of administration: Emulsion for infusion (intravenous use)

Batch number(s): no participants were enrolled, therefore no product was administered

Duration of treatment: 3 days or release from ICU

Reference therapy:

Product name(s): standard nutrition therapy (including enteral and parenteral feeding) Dose: not applicable Mode of administration: enteral, parenteral Batch number(s): no participants were enrolled, therefore no product was administered
Statistical methods: Descriptive statistics (mostly rates with 95% confidence intervals) will be presented to describe the dose-finding study feasibility outcomes. Safety and pharmacokinetic variables will be described by arm. However, due to the limited sample size and the potential of rolling the dose-finding study into the definitive study, clinical efficacy outcomes will be reported overall but not by arm. This dose-finding study will not be used to determine effect size, but it will provide further information regarding the distribution of our tentative primary outcome that may allow us to further refine our primary outcome and definitive sample size estimation. The primary analysis will follow the intent-to-treat principle including all patients in the arm they were randomized to regardless of treatment compliance.
Treatment Compliance: As the trial participants will exclusively be treated while their ICU stay, no additional measures for compliance were implemented.
Efficacy variables: The primary objective is to determine the feasibility and safety of intravenous FO (0.20 g/kg and 0.50 g/kg IBW) administration in high-risk patients undergoing cardiac surgery. Furthermore, we aim to evaluate the efficacy of FO supplementation on the inflammatory response and the patients` immune system. We will assess the effect of fish oil application on the peri-operative systemic inflammatory response and immune status, measured by interleukin-1 [IL-1], IL-6 and tumor necrosis factor-alpha [TNF-α]. The anti-inflammatory response will be measured by IL-1RA and IL-10. Oxidative stress will be measured by total antioxidant capacity and oxidative reductive potential (ORP). Furthermore, we will analyze the resulting effects of the inflammatory response on the immune system, as measured by phorbolmyristate acetate (PMA) ex-vivo stimulation of tumor necrosis factor-alpha [TNF-α] in whole blood. To further characterize the efficacy effect of fish-oil on the body`s immune competence, we aim to perform flow-cytometry (FACS analysis) to assess the immune phenotype and activation of different immune cells. **Safety variables:** Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of laboratory values, regular measurement of vital signs and the performance of physical examinations. Moreover, we will assess biochemical parameters of safety (i.e. blood lipid levels HDL and LDL profile and plasma triglycerides, coagulation parameters (thrombocyte count, INR and bleeding time)) and markers of organ dysfunction such as Troponin, bilirubin or well-established markers of acute kidney injury such as neutrophil gelatinase-associated lipocalin (NGAL). Number of postoperative bleeding, use of blood products, and occurred adverse and serious adverse events will also be included in the safety outcome assessment.

Data Quality Assurance: A Data Monitoring Committee consisting of international experts with expertise in cardiac surgery, immunomodulation in critical ill patients, and nutrition will periodically monitor the safety reports and other aspects of quality management related to this trial.
Standardization procedures will be implemented to ensure accurate, consistent, complete and reliable data, including methods to ensure standardization within assessors (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, and validation methods).

Risk Evaluation/Protocol Deviations: There were no trial sites initiated and no participants enrolled in the trial. Therefore, no risk evaluation was necessary and no protocol deviations took place.

Safety Evaluation: Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of laboratory values, regular measurement of vital signs and the performance of physical examinations.

Adverse Events: 0

Safety results: As no participants were enrolled in the trial, no adverse events occurred.

Summary of results: n.a., as no participants were enrolled in the trial

Subject disposition: n.a., as no participants were enrolled in the trial

Demographics: n.a., as no participants were enrolled in the trial

Efficacy results: n.a., as no participants were enrolled in the trial

Conclusion: n.a., as no participants were enrolled in the trial

The undersigned authors agree to the content of this clinical study report by giving their signatures. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.

Sponsor
RWTH Aachen, represented by the principal, represented by the Dean of the Medical Faculty
Univ. – Prof. Dr. rer. nat. Stefan Uhlig

Place, Date:

Signature:

Principal Investigator
Prof. Dr. med. Christian Stoppe

Place, Date:

Signature:

Author
Prof. Dr. med. Christian Stoppe

Place, Date:

Signature: