Study Plan of

A RANDOMIZED, CONTROLLED, DOUBLE-BLIND, MULTICENTER CLINICAL TRIAL ON HOME PARENTERAL NUTRITION USING AN OMEGA-3 FATTY ACID ENRICHED MCT/LCT LIPID EMULSION

The HOME Study

(**H**PN WITH **OME**GA-3)

STUDY IDENTIFICATION NO.: HC-G-H-1403

NCT03282955

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Marketing Authorization Holder:

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Germany

Organized and Financed by:

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STUDY OVERVIEW

Title of Study	A randomized, controlled, double-blind, multicenter clinical trial on home parenteral nutrition using an Omega-3 fatty acid enriched MCT/LCT lipid emulsion – The HOME Study (HPN with OMEGA-3)
Investigational Products	Investigational test product: Lipidem® / Lipoplus® 200 mg/ml (in the following referred as Lipidem) Investigational reference product: Lipofundin® MCT/LCT / Medialipide® 20% (in the following referred as Lipofundin MCT)
Phase	IV
Study Design	Prospective, randomized, controlled, double-blind, multicenter clinical trial performed in two parallel groups
Number of Sites & Countries	Up to 15 sites, planned countries: Poland, Belgium, France, Italy, Netherlands, Spain and United Kingdom
Sample Size	160 patients in total (80 per group)
Indication	Supply of energy, including a readily utilizable lipid component (medium-chain triglycerides) and essential omega-6 fatty acids and omega-3 fatty acids, as part of parenteral nutrition when oral or enteral nutrition is impossible, insufficient or contraindicated.
Primary Objective	Proof of safety and tolerability of home parenteral nutrition (HPN) with an Omega-3 fatty acid enriched MCT/LCT lipid emulsion in adult patients with chronic intestinal failure (CIF) in need of long-term HPN
Primary Variable	The primary endpoint of the study is the change of liver function parameters defined as the sum of the N(0,1)-transformed differences in bilirubin, Alanine transaminase (ALT) and Aspartate transaminase (AST) from baseline to visit 2.
Secondary Objectives	Further safety and efficacy evaluation
Secondary Variables	Variables indicated with * are calculated values **Safety** • Hepatic function ▪ Bilirubin (total and conjugated) ▪ Alanine transaminase (ALT) ▪ Aspartate transaminase (AST) ▪ AST/ALT ratio* ▪ Alkaline phosphatase (ALP) ▪ Gamma-glutamyl transpeptidase (GGT) • Blood count and coagulation ▪ White blood cells (WBCs)

	▪ Red blood cells (RBCs) ▪ Hemoglobin (Hb) ▪ Hematocrit (Hct) ▪ Platelets ▪ International normalized ratio (INR) (if not possible prothrombin time [PT = Quick-value] is accepted) ▪ Activated partial thromboplastin time (aPTT) • Other biochemical parameters ▪ Blood glucose ▪ Electrolytes (Na, Cl, K, Ca, Mg, P) ▪ Serum creatinine ▪ Triglycerides ▪ Cholesterol ▪ High-density lipoprotein (HDL) cholesterol ▪ Low-density lipoprotein (LDL) cholesterol ▪ C-reactive protein (CRP) ▪ α-Tocopherol/Vitamin E (facultative if routinely assessed) ▪ Triene:tetraene ratio* obtained from fatty acid pattern in plasma • Adverse events (AEs) **Efficacy** • Fatty acid pattern in plasma and RBCs • BMI* **Other variables** • Demographic data ▪ Age ▪ Gender ▪ Ethnic origin ▪ Body height ▪ Body weight • Anamnesis ▪ Medical history relevant with regard to HPN o Pathological classification of IF

	○ Underlying disease ▪ Concomitant disease(s) ▪ Ongoing medications ▪ Lipid emulsion(s) during the last 6 months ▪ Anamnestic peculiarities • Physical examination • Vital signs • Body weight change* • Quality of life (EQ-5D™) • Concomitant medication • Energy requirements • PN regimen prescription • Treatment compliance* • Intake of oily fish meals • Study termination
Patient Inclusion / Exclusion Criteria	**Inclusion criteria** 1. Signed informed consent available 2. Male or female patients ≥ 18 years of age 3. Patients with chronic intestinal failure receiving HPN including lipids in whom the parenteral macronutrients have not been changed by more than 10% for at least 3 months 4. Patients receiving ≥ 3.0 g lipids/kg body weight per week **Exclusion criteria** 1. Persistent high total bilirubin values in medical history of last 6 months (> 40µmol/l) 2. Patients in whom PN was interrupted for longer than 4 continuous weeks in the preceding 6 months 3. Patients with history of cancer and anti-cancer treatment within the last 2 years 4. Hypersensitivity to egg, fish, peanut or soya-bean protein or to any of the active substances or excipients 5. Patients treated in the past or currently with Teduglutide 6. Contraindications to investigational products (if available from medical records) including: • Severe hyperlipidemia, including severe hypertriglyceridaemia (≥1000 mg/dl or 11.4 mmol/l)

	• Severe coagulopathy • Intrahepatic cholestasis • Severe hepatic insufficiency • Severe renal insufficiency in absence of renal replacement therapy • Acute thromboembolic events • Fat embolism • Aggravating haemorrhagic diatheses • Metabolic acidosis 7. General contraindications to parenteral nutrition (if available from medical records) including: • Unstable circulatory status with vital threat (states of collapse and shock) • Acute phase of cardiac infarction or stroke • Unstable metabolic conditions (e.g. decompensated diabetes mellitus, severe sepsis, coma of unknown origin) • Inadequate cellular oxygen supply • Disturbances of the electrolyte and fluid balance (e.g. hypokalaemia and hypotonic dehydration) • Acute pulmonary edema • Decompensated cardiac insufficiency 8. Positive test for HIV, Hepatitis B or C (from medical history) 9. Known or suspected drug or alcohol abuse 10. Patients who are unwilling or mentally and/or physically unable to adhere to study procedures 11. Participation in another interventional clinical trial in parallel or within three months prior to the start of this clinical trial 12. Any medical condition that in the opinion of the investigator might put the subject at risk or interfere with patients participation For women with childbearing potential (i.e. females who are not chemically or surgically sterile or females who are not post-menopausal) 13. Women of childbearing potential tested positive on standard pregnancy test (urine dipstick) 14. Lactation 15. Women of childbearing potential who do not agree to apply adequate contraception 16. Persons of legal age who are the subject of a legal protection measure or who are unable to express their consent
Investigational Test Product	**<u>Lipidem</u>** 1000 ml emulsion contain: Medium-chain triglycerides 100.0 g Long-chain triglycerides (soybean oil) 80.0 g

	Omega-3 fatty acid triglycerides 20.0 g <u>Essential fatty acids</u> Linoleic acid (Omega-6) 38.4 – 46.4 g Alpha-Linolenic acid (Omega-3) 4.0 – 8.8 g Eicosapentanoic acid (EPA) and Docosahexanoic acid (DHA) 8.6 – 17.2 g Additional excipients are: all-rac-α-Tocopherol, egg lecithin, glycerol, ascorbyl palmitate, water for injections <u>Excipient(s) with known effect</u> Sodium (as sodium hydroxide and sodium oleate) 2.6 mmol/l Energy content 7990 kJ ≈ 1910 kcal Theoretical osmolality approx. 410 mOsm/kg NaOH or HCl for titration to pH 7.4 < 0,5 mmol/l pH 6.5 – 8.5
Investigational Reference Product	**<u>Lipofundin MCT</u>** 1000 ml emulsion contain: Medium-chain triglycerides 100 g Long-chain triglycerides (soybean oil) 100 g <u>Essential fatty acids</u> Linoleic acid (Omega-6) 48.0 – 58.0 g Alpha-Linolenic acid (Omega-3) 5.0 – 11.0 g Additional excipients are: all-rac-α-Tocopherol, egg lecithin, glycerol, sodium oleat, water for injections Energy content 8095 kJ ≈ 1935 kcal Theoretical osmolarity approx. 380 mOsm/l NaOH or HCl for titration to pH 7.4 < 0,5 mmol/l pH 6.5 – 8.5
Investigational Products Administration	**Method of Administration** The administration of the investigational products (IPs) is performed intravenously. **Dosage** IP will be delivered as the lipid part of the parenteral nutrition (PN). Besides the lipid PN contains glucose, amino acids, electrolytes, trace

	elements and vitamins and will be administered according to the individual patient's normal prescription. The weekly dose of IP will be at least 3.0 g lipid per kg body weight (BW) (corresponding 15 ml emulsion per kg BW and week). **Treatment Duration** Treatment with IP is projected for a period of 8 weeks on average and will not end before Visit 2.
Visit Schedule	**<u>Screening</u>** ▪ Preferably during a regular patient monitoring visit ▪ Patient information and signature of informed consent form (patient information sheet might be provided to the patient prior the visit) ▪ Verification of inclusion and exclusion criteria ▪ Pregnancy test (urine dipstick), if applicable **<u>Randomization</u>** ▪ After check of all inclusion and exclusion criteria the patient will be randomized. **<u>Baseline</u>** The baseline assessment is performed after randomization on the day of screening. <u>Documentation of:</u> ▪ Demographic data ▪ Anamnesis ▪ Physical examination <u>Assessment of safety, efficacy and other variables (blood samples will be taken the earliest 3 hours after the last PN infusion):</u> ▪ Vital signs ▪ Laboratory values from routine blood samples • Hepatic function (incl. blood samples for central laboratory analyses of primary variable) • Blood count and coagulation • Other biochemical parameters ▪ Blood samples for central laboratory analyses of fatty acid pattern in RBCs and plasma ▪ QoL ▪ Concomitant medication ▪ AEs continuously from start of study The patient will be provided with a patient diary for documentation of IP

	administration on a daily base. At baseline visit the patient diary will be handed out for the treatment period until visit 1. Prescription of PN including IP: ▪ Treatment with IP will start within one week after baseline visit ▪ If applicable, changes in prescription will be documented continuously throughout the course of the study **Visit 1 = 4 weeks after start of IP infusion** Study visit 1 should be preferably the same day of week and day time as the baseline visit. If this is not possible, it should be the same interval between PN infusion and visit day as it was for baseline (e.g. if baseline visit was after a day free of PN, visit 1 should be after a day free of PN as well). Assessments and procedures: ▪ Pregnancy test (if applicable) Assessment of safety, efficacy and other variables (blood samples will be taken the earliest 3 hours after the last PN infusion): ▪ Vital signs ▪ Body weight ▪ Laboratory results • Hepatic function (incl. blood samples for central laboratory analyses of primary variable) • Blood count and coagulation • Other blood biochemistry parameters ▪ Treatment compliance will be documented in the electronic case report form (eCRF) on the basis of patient diary entries ▪ Concomitant medication ▪ AEs The investigator will collect the first part of the patient diary and check for accurateness and completeness. The data will be enter into the eCRF. A new patient diary will be handed out for the treatment period until visit 2. **Visit 2 (final visit) = 4 weeks after visit 1** Study visit 2 should be preferably the same day of week and day time as the baseline visit (and/or visit 1). If this is not possible, it should be the same interval between PN infusion and visit day as it was for baseline (e.g. if visit 1 was after a day free of PN, visit 2 should be after a day free of PN as well). Assessment and procedures: ▪ Pregnancy test (if applicable) Assessment of safety, efficacy and other variables (blood samples will be taken the earliest 3 hours after the last PN infusion): ▪ Vital signs

	▪ Body weight ▪ Laboratory results • Hepatic function (incl. blood samples for central laboratory analyses of primary variable) • Blood count and coagulation • Other blood biochemistry parameters ▪ Blood samples for central laboratory analyses of fatty acid pattern in RBCs and plasma ▪ QoL ▪ Treatment compliance will be documented in the eCRF on the basis of patient diary entries ▪ Concomitant medication ▪ AEs Patient diary will be collected and data entered in the eCRF Visit 2 is the final study visit for the patient and study termination page of the eCRF will be completed. After this final visit no IP must be administered. The PN treatment will continue according to the decision of the physician with a regularly used lipid emulsion.
Duration of Study per Patient	Start of study: with randomization Treatment period (infusion of IP): ▪ Start of IP infusion within one week after randomization ▪ Treatment with IP is projected for a period of 8 weeks on average and will not end before visit 2 End of study: Final visit (study visit 2)
Study Schedule	Planned start: Q1 / 2018 Planned recruitment time: 5.5 years Planned last patient out: Q2 / 2023
Statistical Methods	Two sample t-test for mean difference assuming equal variances (testing non-inferiority) Descriptive statistics including methods for the comparison of two groups (t-test, U test, $\chi 2$ test)
Randomization / Blinding	Patients will be assigned at a 1:1 ratio to receive either Lipidem or Lipofundin MCT. The allocation to one of the two treatment groups will be performed by permuted block randomization with stratification for study site. The study is double-blind.
Data and Safety Monitoring Board (DSMB)	A DSMB will not be appointed.

Statistical Analysis and Evaluation

Statistical methods

All programming of tables, figures, listings and statistical analyses will be performed using SAS® version 9.4 (or higher). The planned statistics will be performed in accordance with the principles outlined by the guideline ICH E9.

The primary endpoint of the study is the change of liver function parameters defined as the sum of the N(0,1)-transformed differences from baseline in ALT, AST, and bilirubin after 8 weeks of treatment. It is the aim to demonstrate non-inferiority of the primary endpoint with respect to 'deterioration in liver function' using the non-inferiority margin δ=1.151. This margin was derived as 'σ/2' from a previous study on the use of lipid emulsions in HPN patients which provided a standard deviation of 2.3029 for the specified endpoint. The non-inferiority will be shown using the two-sample t-tests for mean differences assuming equal variances under the following conditions:

- distribution : normal
- method : exact
- number of sides: 1
- alpha : 0.025
- mean difference :1.151 (= non-inferiority margin δ).

The primary analysis will be performed for the Valid case set (FAS for sensitivity). No imputation will be performed.

Thus, the t-test will compare the (one-sided) null hypothesis

- H_0: $\Delta_T \geq \Delta_S + \delta$

against the alternative hypothesis

- H_1: $\Delta_T < \Delta_S + \delta$

on the level of 0.025, where Δ_T and Δ_S represent the increase of the primary endpoint upon T=test and S=standard. Non-inferiority (with non-inferiority margin δ=1.151) can be concluded, if the VCAS analysis yields an upper limit of the two-sided 95% confidence interval (or one-sided 97.5% confidence interval) for the treatment contrast of the primary endpoint lower than 1.151 and if this result is confirmed by the corresponding FAS analysis.

Superiority of T vs S, i.e. H_0: $\Delta_T \geq \Delta_S$ vs. H_1: $\Delta_T < \Delta_S$, is demonstrated simultaneously, if the upper limit of the confidence interval is below zero for both the FAS analysis and and the VCAS analysis.

Given the non-inferiority of T vs. S, the following procedure will be performed subsequently:

- breakdown of the multiple primary endpoint to its components ALT, AST, and bilirubin with unchanged level (Lehmacher *et al.,* 1991).

Further methods are descriptive statistics including standard procedures for the comparison of two groups (t-test, U test, χ^2 test).

Interim Analysis

No interim analyses are planned.

Level of significance and power

The primary endpoint will be tested one-sided with an significance level of α=0.025.
Tests of secondary variables will be carried out in the area of exploratory data analysis. Therefore, corresponding p-values are to be regarded as exploratory ones and no adjustments for multiple testing will be made.
Sample size calculation is performed with a power of 80%.

Statistical hypotheses

The higher 'deterioration in liver function' is indicated by a higher sum of the N(0,1)-standardized changes from baseline to visit 2 in ALT, AST and bilirubin. Therefore, the hypotheses specified before will show – in case of significance – that the potential deterioration in liver function is not relevantly higher upon T than upon S.

Data handling

All data will be listed. Whenever applicable all tables, figures and listings will identify patients using the patient identification (ID) and time of evaluation. For data collected prior to randomization, patients will appear in the listings with the treatment to which they were subsequently allocated.

The actual population presented in a table/figure/listing will be mentioned in the headings.

Tables and listings will be produced in accordance with the principles outlined by the ICH E3 guideline.

Handling missing data and outliers

Every effort will be made to collect all data points in the study. The amount of missing data will be minimized by appropriate management of the randomized, prospective, trial, proper screening of subjects, and training of participating investigators and other authorized staff (e.g. nurses), monitors and study co-coordinator. Since all patients who are randomized will be included in the primary analysis, in those instances where data are missing, missing values will not be imputed.

Prior to database lock a blinded data review meeting will be held to identify remaining data issues, review listings/graphs specifically created for the data review meeting, to assess the impact of protocol violations on the interpretation of data and to trigger last database corrections or an SAP update as applicable.

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