Abschlussbericht gemäß § 13 GCP-V

- Synopse -

Version 01, Datum 16.06.2021

The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Randomized Trial

The EFFORTcombo Trial

Controlled, randomized, open, parallel group design

EudraCT Nummer: 2018-003703-19

Vorlage-Nummer: 4043520

Kurztitel: EffortCombo

Sponsor der klinischen Prüfung:
RWTH Aachen, vertreten durch den Rektor, vertreten durch den Dekan der Medizinischen Fakultät Univ.-Prof. Dr. rer. nat. Stefan Uhlig

Leiter der klinischen Prüfung:
PD Dr. med. Christian Stoppe
Department of Intensive Care Medicine,
Uniklinik RWTH Aachen,
Pauwelsstraße 30, 52074 Aachen,
Tel.: 0241/80 36575

Autor des Abschlussberichtes:
PD Dr. med. Christian Stoppe
Department of Intensive Care Medicine,
Uniklinik RWTH Aachen,

Prüfer	Prüfzentrum	EudraCT
PD Dr. med. Christian Stoppe	UK Aachen	2018-003703-19

Pauwelsstraße 30, 52074 Aachen,
Tel.: 0241/80 36575

Unterschriften

Die unterzeichnenden Autoren stimmen den Inhalten des vorliegenden Abschlussberichtes durch ihre Unterschriften zu. Die hier berichtete, klinische Prüfung wurde nach den Grundsätzen der Deklaration von Helsinki, der Guten Klinischen Praxis (GCP) sowie den geltenden Gesetzen durchgeführt.

Sponsor / Vertreter
RWTH Aachen, vertreten durch den Rektor, vertreten durch den Dekan der Medizinischen Fakultät Univ.-Prof. Dr. rer. nat. Stefan Uhlig

Unterschrift _____ Ort, Datum _____

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Handelsname des Arzneimittels	**PR1: Olimel®** **PR2: PeriOlimel®**
Wirkstoff/ Aktive Substanz	Parenteral nutrition formula provided in a three-chamber bag The three chambers contain the following drug substances: dextrose solution, amino acid solution with electrolytes (sodium, potassium, magnesium, phosphate) and lipid emulsion (mix of refined olive oil and refined soybean oil)
Titel der Studie	The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Randomized Trial
Prüfer der klinischen Prüfung	PD Dr. med. Christian Stoppe Department of Intensive Care Medicine Uniklinik RWTH Aachen Dr. Stefan Schaller Department of Anesthesiology and Intensive Care Technische Universität München PD Dr. Gunnar Elke Department of Anesthesiology and Intensive Care Medicine Uniklinikum Kiel
Studienzentrum/-zentren:	Uniklinik RWTH Aachen Department of Intensive Care Medicine Pauwelsstraße 30, 52074 Aachen Universitätsklinikum Schleswig-Holstein, Campus Kiel Department of Anesthesiology and Intensive Care Medicine Arnold-Heller-Straße 3, 24105 Kiel Technische Universität München Department of Anesthesiology and Intensive Care Ismaninger Straße 22, 81675 München
Publikationen	none
Studienzeitraum	First-Patient-In: n.a.

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	Last-Patient-Out: n.a. In this study no patients were recruited. The study duration per patient is 6 months.
Phase der klinischen Prüfung	III
Art des Vorhabens	Intervention group: Enteral Nutrition + supplemental Nutrition (protein target ≥ 2.2 g/kg/d) Control group: Enteral Nutrition alone (Standard Care) (protein target ≤ 1.2 g/kg/d) The infusion rate will start with 25 ml/hr and increased as tolerated (e.g. every 4-6 hours) so that 100% of the nutrition goals are reached after 24-48 hours. If protein target cannot be met by combined enteral/parenteral nutrition (EN/PN), protein supplements (EN powder or i.v.) should be added as per local standards to reach the goal of ≥2.2 g/kg /d. The control group will receive standard enteral nutrition only with a protein target of ≤ 1.2 g/kg/d In both groups, targets will be set using pre-Intensive Care Unit (ICU) dry actual weight. For patients with body mass index (BMI) >30, ideal body weight based on a BMI of 25 will be used.

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	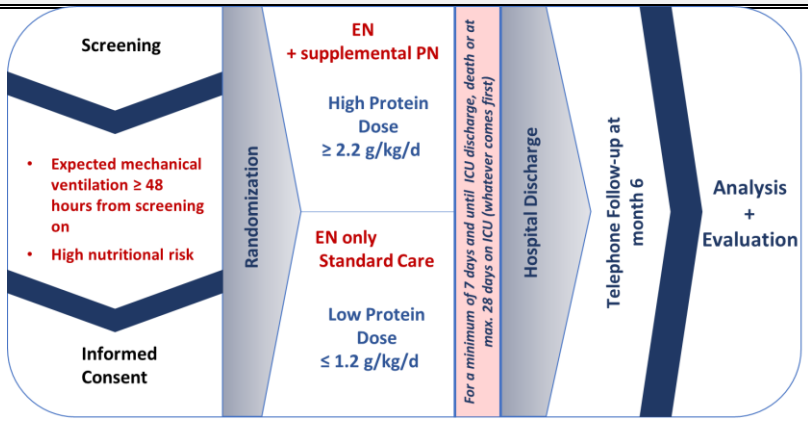
Studienziele	To show the effect of providing combined EN/PN to the group prescribed a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration compared to a low group prescribed ≤1.2 gram/kg/day (EN only) on patient's functional recovery as measured by 6-minute walk distance just prior to hospital discharge.
Primärer Zielparameter	Physical Functioning by 6-minute walk test, evaluated at hospital discharge
Sekundäre Zielparameter	• Overall strength-upper and lower extremity • Quadriceps force-lower extremity strength • Distal strength-hand grip strength • Overall Physical Functional status • Discharge location (e.g. home vs. rehab) • Body composition via Ultrasound • Body composition via CT (when clinically available) • Health-related quality of life • Physical functioning • Healthcare resource utilization

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Studiendesign	This is a multicenter, randomized clinical trial with controlle, open and parallel group design.
Prüfmedikation / Behandlungsstrategie	Trade name: PR1: Olimel®, PR2: PeriOlimel® Active Substance: Parenteral nutrition formula provided in a three-chamber bag The three chambers contain the following drug substances: dextrose solution, amino acid solution with electrolytes (sodium, potassium, magnesium, phosphate) and lipid emulsion (mix of refined olive oil and refined soybean oil) Dosage: ≥200 mg/kg Indication: Olimel® (for intravenous i.v. administration) and PeriOlimel® (for peripheral administration) are indicated for parenteral nutrition for adults when oral or enteral nutrition is not possible, insufficient, or contraindicated. Administration: Olimel® will be administered using a central line. PeriOlimel®, however, is a product that can be used either peripherally or centrally. Batch number: n.a.
Behandlungsdauer	For a minimum of 7 days and until ICU discharge, death or at maximum 28 days on ICU (whatever comes first)
Vergleichsbedingung/ -medikation	n.a. The control group will receive standard enteral nutrition only with a protein target of ≤ 1.2 g/kg/d.
Gesamtzahl Patienten	planned: 142 screened: n.a. enrolled and randomized: n.a. Drop-outs: n.a. No patients were enrolled in this study.

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Studienpopulation	Nutritionally high-risk critically ill, mechanically ventilated adult patient
Einschlusskriterien	1. ≥18 years old; 2. Expected to remain mechanically ventilated for an additional 48 hours from screening; 3. And have one or more of the following risk factors that make them at high nutritional risk: a. Low (≤25) or High BMI (≥35) b. Moderate to severe malnutrition (as defined by local assessments). We will document the means by which sites are making this determination and capture the elements of the assessment (history of weight loss, history of reduced oral intake, etc.). c. Frailty (Clinical Frailty Scale 5 or more from proxy) d. Sarcopenia (SARC-F score of 4 or more from proxy) e. From point of screening, projected duration of mechanical ventilation >4 days1. ≥18 Jahre
Ausschlusskriterien	1. >96 continuous hours of mechanical ventilation before enrollment 2. Expected death or withdrawal of life-sustaining treatments within 7 days from screening 3. Pregnancy 4. The responsible clinician feels that the patient either needs low or high protein 5. Absolute contraindication to EN

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	6. Severe metabolic disorders including electrolyte disorders, uncontrolled hyperglycemia, hyperlipidemia, hypophosphatemia. 7. Severe chronic liver disease (MELD-score >20) or acute fulminant hepatitis. 8. Metabolic disorders involving impaired nitrogen utilization 9. Hypertriglyceridemia-associated acute pancreatitis 10. Known allergy to maize or maize products 11. Known hypersensitivity to hen's egg, soybean products, olive products or an active ingredient, other constituents or components of containers 12. Not ambulating independently prior to illness that lead to ICU admission (use of gait aid permitted) 13. Lower extremity injury or impairments that prevents them walking prior to hospital discharge (e.g. amputation, knee/hip injury) 14. Pre-existing cognitive impairment or language barrier that prohibits outcomes assessment 15. Pre-existing primary severe systemic neuromuscular disease resulting in severe weakness pre-ICU (e.g., Guillain Barre) 16. Intracranial or spinal process affecting motor function 17. Patients in hospital >5 days prior to ICU admission 18. Severe underweight (BMI<18)
<u>Kriterien zur Bewertung der</u> Sicherheit	Patients will be monitored daily for unexpected serious adverse events until death or discharge and SAEs will be reported by the participating site to Aachen (Germany) within the established timelines i.e. an initial report within 24 hours

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	and a follow up report within 10 days of becoming aware of the event. Serious adverse events thought to be related to the IP will be reported by Aachen to the regulatory authorities, respectively, and the manufacturer of the investigational product in an expedited manner within the necessary timelines. Serious adverse events that are not related to the study product will be reported to the manufacturer, applicable regulatory agencies and all participating sites annually. Other events will be reported by the participating sites to their regulatory bodies, according to local requirements, as needed. In addition, the sponsor shall make available to the manufacturer promptly such records as may be necessary and pertinent to investigate any such expedited unexpected serious adverse event, upon request by the manufacturer. Medical interventions / hospital stays planned before the start of the study (e.g. planned revision of an inguinal hernia, hospital stay as part of chemotherapy for pre-existing malignancy) must also be documented as AE or SAE - provided there is no worsening of the disease existing at the start of the study - but not reported to the sponsor.
<u>Kriterien zur Bewertung der</u> Wirksamkeit	See primary and secondary endpoints
Statistische Methoden:	All analyses will be performed using SAS and will follow the intention-to-treat principle. A 2-tailed p-value <0.05 will be considered statistically significant. For this sub-study, the 6MWD will be compared between the 2 groups using the rank-based Mann-Whitney U test. This approach allows inclusion of randomized patients, per the intent-to-treat principle, by assigning decedents a lower value

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	than all survivors (e.g. -1) and assigning patients incapable of performing the 6MWD test a value of 0. In addition to this rank-based test, we will describe the differences in 6MWD between the two groups graphically. Time from randomization to 6MWD testing will be described by arm, and a sensitivity analysis will adjust for the time to testing before comparing the adjusted ranked 6MWD between arms. As secondary outcomes will be considered hypothesis-generating, we will not formally correct for multiple comparisons but will consider the number of secondary comparisons when interpreting our results. Secondary continuous outcomes will be analyzed as described above. Categorical secondary outcomes will include death and unable-to-perform as potential categories and will be analyzed using Fisher's exact tests. The number of missing values will be described for all variables. If >5% of outcome data are missing, multiple imputation will be used for the primary analysis and a "missing not at random" sensitivity analysis will be performed using the tipping point approach of the pattern mixture model with multiple imputation, as per the SAS MI procedure.
Wesentliche Prüfplanänderungen:	none

Summary:

Efficacy and safety results: As no patients were enrolled in this study, the evaluation of results is not applicable.

Conclusion:

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After approval by the competent authorities, this planned trial was not conducted. No site was activated and no patients were included to the trial as the medical faculty of the University RWTH Aachen, was not able to fulfill the Sponsors role due to lack of expertise in multinational studies. Furthermore there were some issues to develop necessary structures within the Center for Translational and Clinical Research (CTC-A) in regards to lack of resources hence it was decided to transfer the sponsorship to the University Würzburg.

The upcoming COVID-19 pandemic (since begin of 2020) in addition to the described complications further hampered the feasibility of this study. Therefore, the joint decision was made to terminate this study before initiation.