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A single-center exploratory trial evaluating the pharmacokinetic profile and the metabolic effects of a ketone ester food supplement in intensive care patients: The KETOCARE 2 trial

Submission date 13/10/2025	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 12/11/2025	**Overall study status** Ongoing	[ ] Statistical analysis plan [ ] Results
Last Edited 12/11/2025	**Condition category** Other	[ ] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Critically ill patients often develop muscle weakness and muscle loss during their stay in intensive care, which hinders recovery and is associated with long-term morbidity and mortality. Research in mice with sepsis showed that continuous intravenous administration of the ketone ester 3-hydroxybutyrate (3HHB) reduced the development of muscle weakness without organ damage or liver toxicity. In previous studies in critically ill patients, 3HHB was administered semi-continuously for one day and was found to be well tolerated. Based on these previous studies, a pharmacokinetic model was developed.
The aim of this study is to investigate whether prolonged ketone ester administration can safely induce ketosis for five days to critically ill patients.

Who can participate?
Adult patients admitted to the intensive care unit at UZLeuven

What does the study involve?
We will investigate the feasibility and safety of enteral 3HHB administered during five consecutive days in ICU. We are therefore planning a monocentric exploratory study in which we will evaluate the dosing regimen proposed by the pharmacokinetic model. Ten critically ill patients will receive 3-hydroxybutyrate via a gastric tube every 2 hours and a total of 7 doses per day. This will be followed by a 12-hour therapy-free interval after the last dose to prevent accumulation. Blood samples will be taken at predetermined times to monitor plasma levels of 3HB and 3HHB (metabolites).

What are the possible benefits and risks of participating?
There are no known interactions of ketone esters with drugs. Over six days a total of 172 ml blood will be collected for analysis. This small amount should not cause any problems and will be taken via a catheter that is already in place.

When is the study starting and how long is it expected to run for?
August 2025 to August 2027

Who is funding the study?
1. European Research Council (ERC)
2. Flemish Government (Belgium)

Who is the main contact?
Prof. Dr. Greet Van den Berghe, greet.vandenberghe@kuleuven.be

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
S70969

Study information

Scientific Title
A single-center exploratory trial evaluating the pharmacokinetic profile and the metabolic effects of a ketone ester food supplement in intensive care patients: The KETOCARE 2 trial

Acronym
KETOCARE 2

Study objectives
To explore the efficacy of the dosing regimen of enteral ketone esters R-3-hydroxybutyl-R-3-hydroxybutanoate (3HHB) derived from the PK-model to induce sustained ketosis.

To demonstrate that prolonged, intermittent supplementation of enteral ketone esters over five consecutive days is safe.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/09/2025, Ethics Committee Research UZ/KU Leuven (Herestraat 49, Leuven, 3000, Belgium; +32 16 34 86 00; ec@uzleuven.be), ref: S70969

Study design
Mono-centric interventional non randomized

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Safety of prolonged, intermittent supplementation of enteral ketone esters in critically ill adult patients

Interventions
Ten critically ill patients will all receive 3-hydroxybutyrate via a gastric tube every 2 hours, for a total of 7 doses per day. This will be followed by a 12-hour therapy-free interval after the last dose to prevent accumulation. Blood samples will be taken at predetermined times to monitor plasma levels of 3HB and 3HHB (metabolites).

Intervention Type
Supplement

Primary outcome(s)
Percentage of plasma 3-hydroxybutyrate concentrations above 1 mmol/L during the 16-hour treatment interval (from first bolus to the expected complete clearance of 3HB, 4h post last bolus), measured by LC-MS/MS

Key secondary outcome(s))
1. Plasma 3-hydroxybutyrate levels during the 6 day intervention window (E), measured by LC-MS /MS
2. Plasma levels of 3HHB and metabolite 1,3-butanediol during the 6 day intervention window (E), measured by LC-MS/MS
3. Urine levels of 3HHB, 3-hydroxybutyrate and 1,3-butanediol during the 6 day intervention window (E), measured by LC-MS/MS
4. Blood glucose concentrations during the 6 day intervention window (E), measured by blood-gas-analyzer on ICU
5. Incidence of severe (<40 mg/dl) hypoglycemia during the 6 day intervention window (S), measured by blood-gas-analyzer on ICU
6. Incidence of ketoacidosis during the 6 day intervention window, defined as a new onset metabolic acidosis with arterial pH less than 7.25 and serum bicarbonate less than 15 mmol/L occurring simultaneously with a 3HB level of at least 10 mmol/L (S), measured by blood-gas-analyzer on ICU
7. Incidence of 3HB levels exceeding 10 mmol/L at any time, without concomitant acidosis, during the 6 day intervention window (S), measured with a ketone stick test on arterial blood in the ICU
8. Incidence of accumulation (pre-administration trough levels exceeding 5 mmol/L) without ketoacidosis during the 6 day intervention window (S), measured with a ketone stick test on arterial blood in the ICU
9. Plasma levels of cholesterol (HDL, LDL, total), triglycerides, free fatty acids over time during the 6 day intervention window (E), measured by commercial kits
10. Plasma levels of bilirubine, gamma-glutamyltransferase, aspartate transaminase and alanine transaminase over time during the 6 day intervention window (S), measured by commercial kits

Completion date
13/08/2027

Eligibility

Key inclusion criteria
1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained
2. At least 18 years of age at the time of signing the Informed Consent Form (ICF)
3. Patient expected to stay at the ICU for at least 6 days after start of the first 3HHB administration
4. The presence of a gastric feeding tube

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Mixed

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Therapy restriction code
2. Patients refusing blood transfusion upon ICU admission will be considered as having a therapy restriction upon admission and will not be included
3. Expected to die within 48 hours after screening (= moribund patients)
4. No arterial and central venous line, or expected to have one of these lines removed before the end of the study period (= not critically ill enough to be representative for the future target population, and no possibility to take blood samples without additional venapuncture)
5. Contraindication for enteral drug administration
6. Readmission to the ICU after previous inclusion in the RCT
7. Inborn metabolic disease
8. Clinical need for a ketogenic diet in ICU
9. Underweight (BMI< 18.5 kg/m²) or admitted with complications due to anorexia nervosa
10. Known to be pregnant or lactating
11. ICU admission with diabetic ketoacidosis or hyperosmolar hyperglycemic state
12. Acute or acute on chronic liver failure
13. High intravenous glucose need to prevent spontaneous hypoglycemia
14. Metabolic acidosis (pH <7.30 and bicarbonate <18 mmol/l)

Date of first enrolment
27/10/2025

Date of final enrolment
27/10/2026

Locations

Countries of recruitment
Belgium

Study participating centre

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Sponsor information

Organisation
Universitair Ziekenhuis Leuven

ROR
https://ror.org/0424bsv16

Funder(s)

Funder type
Government

Funder Name
European Research Council

Alternative Name(s)
The European Research Council, ERC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
Flemish Government Methusalem Program

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository (name: RDR; https://rdr.kuleuven.be/)

IPD sharing plan summary

Stored in publicly available repository