Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 3 Doses of MOTREM in Patients with Septic Shock. A Randomised, Double-blind, Two-stage, Placebo Controlled Study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45445

Source
ToetsingOnline

Brief title
N/A

Condition

- Other condition

Synonym
Blood infection; complication of Sepsis leading to life threatening drop in blood pressure

Health condition

Intensive care - septic shock

Research involving
Human

Sponsors and support

Primary sponsor: INOTREM S.A
Source(s) of monetary or material Support: INOTREM S.A

Intervention

Keyword: MOTREM (LR12), Septic Shock

Outcome measures

Primary outcome

Safety and tolerability parameters:

1. Vital signs: systolic (SBP) and diastolic (DBP) blood pressure, heart rate,

and body temperature (tympanic)

2. ECG (12-lead ECG)

3. Safety laboratory tests: haematology, coagulation, plasma biochemistry

4. Presence of anti-LR12 antibodies

5. Adverse events : from screening until study completion

Secondary outcome

Pharmacokinetics:

Plasma concentrations of LR12 will be measured by a validated LCMS/MS assay and

analysed using non-compartmental methods to obtain

estimates of the PK parameters.

Pharmacodynamics (exploratory)

The concentration profiles of biomarkers (sTREM-1, immune and vascular related

biomarkers) over time and biomarker mRNA levels will

be analysed.

Clinical parameters (exploratory)

1. Resolution of organ dysfunction (SOFA score total and individual domains)

2. Vasopressor use

3. Invasive mechanical ventilation

4. Renal support

5. Time until shock reversal defined as cessation of vasopressor support for 24

hours

6. Mortality at day 28 and Day 90

Study description

Background summary

Sepsis is an inflammation of the body secondary to an acute infection which can be life-threatening. Sepsis occurs when chemicals released into the bloodstream to fight the infection trigger defense responses throughout the body. Anyone can develop sepsis, but the risk is higher in older adults or those with weakened immune systems. If sepsis progresses to septic shock, blood pressure drops dramatically with multiple organ consequences and an increased mortality. An uncontrolled and overwhelming immune response is thought to be contributing to high number of deaths in patients with septic shock. Sepsis and septic shock is the most frequent cause of death in intensive care units (ICUs) and is the 11th leading cause of death worldwide. To date, people with sepsis are treated with antibiotics to kill the bacteria responsible for the infection and other general medications and procedures based on symptoms but no specific therapy is currently available for septic shock.

MOTREM is an investigational new drug which has been developed by a pharmaceutical company called INOTREM SA (the Sponsor). MOTREM is a chemically synthesised peptide (small protein) that prevents amplification of the immune response that can lead to the start and progression of sepsis into septic

shock. It inhibits activation of TREM-1 (a protein expressed on certain circulating white blood cells). MOTREM has the potential to reverse sepsis-related over-inflammation. Previous non-clinical studies showed that MOTREM is able to control the immune system and to diminish the damage linked to septic shock

Study objective

The objectives of the study are to:
-To evaluate the safety and tolerability of MOTREM in patients with septic shock.
-To evaluate the effects of MOTREM exposure over up to 5 days in patients with septic shock
-To evaluate the PK/PD and dose/PD relationship to TREM-1 pathway related markers
-To evaluate the effect of MOTREM on transcriptomics
-To evaluate the effect of MOTREM on clinical parameters (e.g. vasopressor doses, vasopressor-free days, ventilator-free days, mortality)

Study design

This is a randomised, double-blind, two-stage, placebo controlled study. It consists of 2 stages with a similar treatment regimen, in which 0.3, 1.0 or 3.0 mg/kg/h of MOTREM is tested versus placebo.

After screening for eligibility, patients will be randomised to one of the treatment arms. They will then either receive a 5 mg/kg loading dose of MOTREM over 15 minutes followed by a continuous i.v. infusion of MOTREM or a matching placebo on top of standard of care.

Treatment with study drug must be initiated as early as possible, but no later than 24 hours after the onset of septic shock, defined by the start of vasopressor therapy. Blood samples for the determination of MOTREM (LR12) plasma concentrations and exploratory pharmacodynamic analyses will be collected before and throughout the treatment period.

Patients will be treated until 12 (±2) hours after the resolution of their septic shock (defined as vasopressor withdrawal) with a maximum treatment duration of 5 days (120 hours).The survival status of patients after 28 and 90 days will be collected.

Stage 1 investigates multiple ascending doses of MOTREM or placebo in a sequential design in cohorts of 4 patients (3:1 randomisation). After completion of a cohort (for up to 5 days of infusion), safety and PK data will be reviewed by an independent data safety monitoring board (DSMB) and the study will progress to the next cohort/stage.

Stage 2 investigates 3 doses of MOTREM in a randomised, balanced, parallel-group design involving up to 3 doses of MOTREM and a placebo arm. Only dose arms of MOTREM considered to be safe and well tolerated during Stage 1 will be administered in Stage 2.

Intervention

Stage 1 is investigating multiple ascending doses of MOTREM or placebo in a sequential design in cohorts of 4 patients (3:1 randomisation).
Stage 2 investigates 3 doses of MOTREM in a randomised, balanced, parallel-group design involving up to 3 doses of MOTREM and a placebo arm.

Study burden and risks

There are no known side effects of MOTREM treatment.

To date, MOTREM has been administered to 27 healthy people (volunteers) MOTREM in a previous research trial. MOTREM was considered safe and well tolerated up to the highest dose tested. All reported adverse events in that study were mild and considered unrelated to study drug. Based on non-clinical studies and the clinical study in healthy volunteers it is expected that MOTREM will be safe and well tolerated.

However, side effects of MOTREM treatment may occur. MOTREM has not been given to septic shock patients prior to this study and one of the reasons for this study is to learn more about the possible side effects of MOTREM. There may be risks that we cannot predict, or rare or unknown side effects that could occur.

This study is conducted in hospitals experienced in the treatment of patients with septic shock and with close medical supervision of patients. The potential risks associated with the participation in this research trial will be explained to subjects (or the legally authorised representative) before the decision to participate or not. The medical and nursing staff will follow the subject's condition closely from the onset of septic shock and look for as well as treat any possible adverse event.

Other risks of taking part in this trial:

Sometimes people may experience rare sensitivity/allergic reactions to medications. A sensitivity/ allergic reaction may include: itching; rash; hives; difficulty breathing; tightness in the chest; swelling of your face, lips, mouth, or tongue; wheezing. However, no allergic reactions to MOTREM occurred in any prior trial.

The subject may experience some temporary discomfort, bruising, or rarely, infection at the site of a needle stick, in the process of drawing blood

samples or inserting a catheter into your vein.

MOTREM is a peptide (small protein) which means that the body can potentially recognise it as a foreign body and form antibodies to it. The possibility that the subject reacts against MOTREM is very low since this experimental drug is derived from a normal protein of the body. However, this possibility still exists. Blood samples will be collected throughout the study to assess the development of MOTREM antibodies (immunogenicity tests). Should the subject develop anti-drug-antibodies, he/she will be followed up for at least 3 months or until the antibody response is no longer detected and any adverse effect linked to this reaction will be treated.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide written informed consent (proxy/legal representative/independent physician/emergency consent) according to local regulations
2. Age 18* to 80 years
* 16 to 80 years in the Netherlands
Sepsis
3. Documented or suspected infection: lung, abdominal or elderly UTI (*65 years)
4. Organ dysfunction defined as acute change in SOFA score * 2 points
Shock
5. Refractory hypotension requiring vasopressors to maintain MAP *65mm Hg despite adequate volume resuscitation of at least 20 ml/kg within 6 hours (according to Surviving Sepsis guidelines, see Appendix 1)
6. Hyperlactatemia (blood lactate >2 mmol/l or 18 mg/dl). This criterion must be met at least once for the purpose of diagnosis within the 24 hours before study drug administration

Exclusion criteria

1. Previous episode of septic shock (vasopressor administration) within current hospital stay
2. Underlying concurrent immunodepression (specified in appendix 2)
3. Solid organ transplant requiring immunosuppressive therapy
4. Known pregnancy (positive serum pregnancy test)
5. Prolonged QT syndrome (QTc * 440 ms)
6. Shock of any other cause, e.g. hypotension related to gastrointestinal bleeding
7. Ongoing documented or suspected endocarditis, history of prosthetic heart valves
8. End-stage neurological disease
9. End-stage cirrhosis (Child Pugh Class C)
10. Acute Physiology And Chronic Health Evaluation (APACHE) II score * 34
11. End stage chronic renal disease requiring chronic dialysis
12. Home oxygen therapy on a regular basis for > 6 h/day
13. Severe obesity (BMI * 40)
14. Recent CPR (within current hospital stay)
15. Moribund patients
16. Decision to limit full care taken before obtaining informed consent
17. Participation in another interventional study in the 3 months prior to randomisation

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not available
Generic name:	Not available

Ethics review

Approved WMO Date:	05-04-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2017

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-005032-14-NL
CCMO	NL61182.091.17