

A phase I trial of intravenously administered M6229 in critically ill sepsis patients

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23213

Source

Nationaal Trial Register

Brief title

HistoSeps

Health condition

Adult patients with sepsis in the intensive care unit (ICU).

Sponsors and support

Primary sponsor: Amsterdam UMC, location AMC

Source(s) of monetary or material Support: Health~Holland

Intervention

Outcome measures

Primary outcome

Our primary objectives are:

1. To evaluate the safety, tolerability and pharmacokinetics of intravenously (IV) administered M6229 in critically ill patients with sepsis with specific attention to anti-

coagulation effects (based on changes in activated partial thromboplastin time (aPTT)).

2. To evaluate the pharmacodynamic effect of different doses of M6229 by assessing plasma levels of extracellular histones in the study patients, before and at different time-points after M6229 administration.

Secondary outcome

Secondary objectives:

1. To evaluate the pharmacodynamic effect of different doses of M6229 by assessing plasma levels of other biomarkers of inflammation and endothelial cell damage in the study patients, before and at different time-points after M6229 administration.

2. To correlate changes in histones and other biomarkers with plasma levels of M6229 (PK/PD).

3. To correlate changes in aPTT with plasma levels of M6229 (PK/PD safety)

4. To assess a selection of clinical outcome parameters.

5. Urine pharmacokinetic parameters of M6229.

6. To compare the collected data of patients infused with M6229 with historic controls, using data from the MARS cohort.

Study description

Background summary

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Mortality is high and survivors frequently suffer from long-term sequelae.

Extracellular histones have been identified as essential mediators in the pathogenesis of sepsis and septic shock. These toxic molecules are released by damaged cells in response to infection and high extracellular levels can induce tissue injury and multiple organ dysfunction syndrome. Extracellular histones can be neutralized by complexation with the new candidate drug called M6229, a non-anticoagulant heparin, allowing the use of elevated dose levels relative to regular unfractionated heparin. This project aims at the roll-out of a first-in-man clinical study in sepsis patients evaluating the safety, tolerability, pharmacokinetics and pharmacodynamic effects of intravenously administered M6229 in subjects suffering from sepsis.

Study objective

The hypothesis is that intravenous administration of M6229 is safe to use in subjects with sepsis admitted to the ICU and will rapidly capture circulating histones .

Study design

1. Before M6229 infusion
2. During M6229 infusion

3. Up to 72 hours after start M6229 infusion
4. 30 day follow-up

Intervention

Continuous intravenous infusion of M6229, a low-anticoagulant fraction of heparin. Dose-escalation is based on a modified continual reassessment method (mCRM) including escalation with overdose control (EWOC).

Contacts

Public

Amsterdam UMC, location AMC
Niels van Mourik

020 5669111

Scientific

Amsterdam UMC, location AMC
Niels van Mourik

020 5669111

Eligibility criteria

Inclusion criteria

1. Male or female patients aged ≥ 18 years old.
2. Signed informed consent by patient or legal representative.
3. ICU admittance for sepsis defined by the Sepsis-3 criteria as a life-threatening organ dysfunction caused by a dysregulated host response to an infection.
Organ dysfunction is defined by 1 of the following:
 - a. Increase in SOFA score of ≥ 2 .
 - i. The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction.
 - b. Acute kidney injury
 - i. Defined as $\text{eGFR} < 15 \text{ mL/min}$.
 - c. Acute respiratory distress syndrome
 - i. Defined by the Berlin criteria.
 - d. The need of mechanical ventilation.
 - e. Alteration in mental status.
4. The patients have to be included in the study within 72 hours of ICU admission due to

sepsis. M6229 has to be administered within 84 hours after ICU admission due to sepsis.

Exclusion criteria

1. Subject has an advance directive to withhold life-sustaining treatments.
2. Subject is breastfeeding or intends to get pregnant within 30 days of enrolling into the study.
3. Subject is of childbearing potential and has a positive pregnancy test.
 - a. A woman is considered to be of childbearing potential under the age of 60 years, unless surgically sterile.
4. Clinical suspicion or confirmation of a viral hemorrhagic shock syndrome including, but not limited to, dengue fever.
5. Bleeding risk:
 - a. Clinical:
 - i. Active bleeding;
 - ii. Head trauma;
 - iii. Intracranial surgery or stroke in the past 3 months;
 - iv. History of intracerebral arteriovenous malformation, cerebral aneurysm or mass lesions of the central nervous system;
 - v. Cerebral haemorrhage;
 - vi. History of a bleeding diatheses;
 - vii. Gastrointestinal bleeding in the past 6 weeks;
 - viii. Presence of an epidural or spinal catheter;
 - ix. Contraindication for IV therapeutic UFH.
 - b. Laboratory:
 - i. Platelet count $<50 \times 10^9/L$;
 - ii. INR >2.0 ;
 - iii. Baseline aPTT ≥ 45 seconds prior to enrolment, 1.5x upper limit of normal (ULN).
6. Use of any of the following treatments:
 - a. UFH to treat a thrombotic event within 12 hours before enrolment;
 - b. LMWH at a higher dose than recommended for prophylactic use within 12 hours before the infusion;
 - c. Warfarin (if used within 7 days before study entry AND if the INR exceeds 2.0 at enrolment);
 - d. Direct oral anticoagulant (DOAC) use 3 days prior to enrollment.
 - e. Thrombolytic therapy within 3 previous days;
 - f. Use of IIb/IIIa inhibitors within the previous 7 days.
7. Confirmed antiphospholipid syndrome.
8. Known allergy to fish.
9. Cardiopulmonary resuscitation in the previous 7 days.
10. Liver failure defined as Child-Pugh Score Class C.
11. Abnormal liver function (ASAT and/or ALAT > 5 times upper limit of normal (ULN))..
12. Extracorporeal membrane oxygenation (ECMO) support dependent.
13. Pulmonary embolism or clinical suspicion of deep venous thrombosis (DVT).
14. Life expectancy of less than 24 hours.

15. Treating physician refusal.
16. Known adverse reaction to UFH, including heparin induced thrombocytopenia (HIT).
17. Participation in any other investigational drug study or other interventional study with interfering endpoints.
18. Any other clinical condition which, in the opinion of the investigator, would not allow safe completion of the protocol.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	N/A: single arm study
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	13-09-2021
Enrollment:	16
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion	
Date:	29-08-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 51932

Bron: ToetsingOnline

Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9681
CCMO	NL77116.000.21
OMON	NL-OMON51932

Study results