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

No registrations found.

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

## Summary

### ID

NL-OMON23213

**Source**
NTR

**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

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# 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 eGFR < 15 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 intents 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 x109/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

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|---|---|
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non controlled trial |
| 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

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|---|---|
| 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