A phase I trial evaluating the safety, tolerability and pharmacokinetics of intravenously administered M6229 in critically ill sepsis patients - *HistoSeps*

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Primary Objectives: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...

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

Summary

ID

NL-OMON51932

Source
ToetsingOnline

Brief title
HistoSeps

Condition

- Other condition
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Sepsis, severe infection leading to organ dysfunction

Health condition

Sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Health Holland TKI

Intervention

Keyword: Histones, M6229, Phase I study, Sepsis

Outcome measures

Primary outcome

Safety:

1. Anti-coagulation effects of M6229 determined by a change in aPTT at

different time points during and after infusion of M6229.

Pharmacokinetics:

1. Plasma pharmacokinetic parameters of M6229. The following pharmacokinetic

parameters will be determined by non-compartmental analysis: Cmax, Css,Tmax,

AUC, Clearance, terminal half-life and volume of distribution.

Efficacy:

1. Change in histone plasma levels before and at different time-points after

M6229 administration.

Secondary outcome

Safety:

1. Incidence of excessive anti-coagulation effects

a. Clinical evidence or suspicion of severe non-surgical bleeding, defined as

the administration of >= 2 units of blood products in 24 hours from start of infusion;

b. aPTT > 90 seconds.

2. Adverse reactions that are considered definitely and probably related to M6229 as specified in the protocol.

3. Changes in laboratory tests that are considered definitely and probably related to M6229.

4. Changes in vital parameters that are considered definitely and probably related to M6229.

5. Changes in ECGs QTc that are considered definitely and probably related to M6229

Pharmacokinetics:

1. Urine pharmacokinetic parameters of M6229.

Efficacy:

1. Change in plasma levels of other biomarkers (of inflammation and coagulation/fibrinolysis) before and at different time-points after M6229 administration.

2. Correlation of histone plasma levels and other biomarkers with M6229 plasma levels (PK/PD).

3. Clinical outcome parameters: organ dysfunction (based on SOFA score, ARDS, AKI, liver function), organ support (mechanical ventilation, renal replacement

therapy, vasopression therapy), ICU and hospital mortality.

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.

Study objective

Primary Objectives:
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 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 design

Study design: Phase I clinical study.

This is a first-in-human, phase I, open-label, multicenter, clinical study to investigate the safety, tolerability and pharmacokinetics of M6229 in critically ill patients with sepsis. A modified continual reassessment method (mCRM) with escalation overdose control (EWOC) will be used to control potential dose related off-target pharmacological effect on coagulation (aPTT) to remain acceptable and estimate a recommended dose level of M6229 for further development. The mCRM with EWOC dose recommendation will solely be based on the modeling of the probability of aPTT being above 90 seconds. The trial will be conducted in the intensive care units (ICUs) of Amsterdam UMC, location AMC and Maastricht UMC+ and aims to enroll 26 patients maximally.

Intervention

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

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This is the first time that M6229 is administered to human subjects, with inherent risks. However, pre-clinical studies with M6229, and pre-clinical and clinical studies with heparins indicate that the risk of side effects is very low. Importantly, the anticoagulant activity of M6229 is 2 orders of magnitude lower than that of unfractionated heparin (UFH), as determined by its activity to inhibit total thrombin generation in human plasma. Therefore, the therapeutic window of M6229 regarding histone neutralising capacity is expected to be greater than the therapeutic window of heparin. Patients will be closely monitored in the ICU by the study investigators and an experienced medical team. Serial coagulation and other biochemistry parameters will be collected frequently during and after infusion and when deemed harmful the administration of M6229 will be ceased immediately. Even though efficacy is not the primary endpoint in this phase I trial, participants might still experience benefit from M6229 administration, as preclinical studies in sepsis animal models demonstrated reduced mortality and organ dysfunction rates when receiving heparins.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patients aged >= 18 year.
2. Signed informed consent by patient or legal representative.
3. Diagnosed with sepsis, defined by the Sepsis-3 criteria as a life-threatening organ dysfunction caused by a dysregulated host response to an infection.
4. The patients have to be included in the study within 72 hours of ICU admission due to sepsis or within 72 hours after sepsis diagnosis on the ICU. M6229 has to be administered within 84 hours after ICU admission due to sepsis or within 84 hours after sepsis diagnosis on the ICU

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 infusion;
b. LMWH within 24 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 [19].
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

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-04-2022
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	M6229
Generic name:	M6229

Ethics review

Approved WMO Date:	21-06-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23213

Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-000328-37-NL
ClinicalTrials.gov	NCT05208112
CCMO	NL77116.000.21
OMON	NL-OMON23213