A Double-Blind, Placebo-Controlled, Randomized, Multicenter, Proof of Concept and Dose-Finding Phase II Clinical Trial to Investigate the Safety, Tolerability and Efficacy of ADRECIZUMAB in Patients with Septic Shock and Elevated Adrenomedullin

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

Summary

ID

NL-OMON48885

Source
ToetsingOnline

Brief title
AdrenOSS-2

Condition

- Other condition
- Hepatobiliary neoplasms malignant and unspecified

Synonym

blood poisoning - sepsis

Health condition

Orgaandisfunctie

Research involving
Human

Sponsors and support

Primary sponsor: Adrenomed AG
Source(s) of monetary or material Support: Adrenomed AG

Intervention

Keyword: Adrecizumab, Adrenomedullin, Early disease onset, Septic shock

Outcome measures

Primary outcome

The primary objective of this study is

* To investigate the safety and tolerability of ADRECIZUMAB in patients with early septic shock and elevated bio-ADM (concentration of > 70 pg/ml) in treatment arm A (2 mg/kg) and in treatment arm B (4 mg/kg) over the 90 days study period.

Endpoints for Primary Objective (Safety and Tolerability):

The endpoints for the primary objective are to determine over the 90 days study period:

* Mortality

* Interruption of infusion

* Severity and frequency of treatment-emergent adverse events

Secondary outcome

The secondary objectives of this study are

* To obtain first data on efficacy of ADRECIZUMAB in patients with early septic shock and a bio-ADM concentration of > 70 pg/ml in the treatment arms compared with placebo.
* To study the PK of free-ADRECIZUMAB with a focus on plasma accumulation and elimination.

Endpoints for Secondary Objective (Efficacy)

The primary efficacy endpoint of this study is the

* Sepsis Support Index (SSI) defined as: days with organ support or dead within 14 day follow up

More precisely: In the time frame of 14 day follow-up, each day on support with vasopressor, and/or mechanical ventilation (defined as any ventilation received on this day, independent from the duration of mechanical ventilation), and/or renal dysfunction (defined as renal SOFA = 4), or not alive, is counted as 1.
The sum over the follow up period is defined as SSI.

Secondary efficacy endpoints include:

* Sepsis Support Index (SSI) at 28 day follow-up
* Penalized Sepsis Support Index (pSSI) at 14 and 28 day follow-up, defined similar to the SSI with the exception that patients that die get penalized by assigning the maximum value, i.e. the pSSI is set to 14 or 28, respectively
* Persistent organ dysfunction or death at 14 and 28 day follow-up [5]
* Day 28 and day 90 mortality rate

* SSI and pSSI excluding the renal component

* Individual Sepsis Support Index components (hemodynamic, respiratory and renal failure) with and without mortality

* Sequential Organ Failure Assessment (SOFA) Score

- Mean/maximum/total daily SOFA score during stay at ICU

- Delta SOFA score, defined as maximum versus minimum SOFA during ICU stay

- Change in SOFA score within 48 hours

- SOFA-3 (score limited to cardiovascular, respiratory and renal function)

* Improvement in renal function as change in penKid and creatinine (day 3 * day 1, day 7 * day 1)

* Duration of stay at ICU/ hospital

* Changes of functional parameters and other parameters during stay at ICU (MAP, creatinine, PaO2/FiO2, blood lactate, fluid balance, MR-proADM, inflammatory markers PCT, IL6)

* Vasopressor use (drug, highest/lowest dose, duration)

* Quality of Life by Euro-QoL-5 (day 28 and day 90)

* Vital signs (heart rate, blood pressure)

Endpoints for Pharmacokinetics

In sub-study (with 80 patients only) to determine key PK parameters, including:

* peak plasma concentrations (Cmax)

* systemic exposure (AUC)

* volume of distribution (V)

* systemic clearance (CL)

* elimination half-life (t*)

Study description

Background summary

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in 2 total SOFA score points subsequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP > 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

One important factor in the pathogenesis of sepsis and septic shock seems to be Adrenomedullin (ADM). It could also be demonstrated that ADM influences the stability of the circulation directly and indirectly: it has direct chronotropic, inotropic and vasodilatory effects. Several in-vitro and in-vivo studies have shown that ADM seems also to be a key regulator of endothelial permeability in sepsis.

A possible mode of action for the anti-ADM antibody ADRECIZUMAB is described as follows:
Due to its small size (about 6 kDa), ADM is supposed to be able to freely diffuse between the blood circulation and the interstitium. The inner wall of blood vessels is composed of endothelial cells. Smooth muscle cells, on the contrary, have no direct contact to the blood circulation, as they are located distal at the basal site of the endothelial cell layer of arteries. Thus, it can be assumed that ADM located in the blood circulation can act on endothelial cells to stabilize endothelial permeability, but from this compartment cannot directly exert its vasodilatory activity on smooth muscle cells. Rather, smooth muscle cells are accessible for ADM, when it is located in the interstitium.
When the anti-ADM antibody ADRECIZUMAB (HAM8101) is administered in the blood circulation at high concentrations by far exceeding those of plasma ADM, the compartmental distribution of ADM is altered. ADRECIZUMAB, an IgG with a molecular weight of more than 150 kDa, is too large to freely diffuse from the blood circulation to the interstitium.
With its fast association kinetics ADRECIZUMAB quickly binds to ADM in the blood circulation and *pulls* ADM, which has been initially located in the interstitium, from this compartment to the blood circulation. The more ADRECIZUMAB is applied, the stronger is the *pulling* effect and the higher the

resulting concentrations of ADRECIZUMAB-bound ADM in the blood circulation. As a consequence of this redistribution, the ADM concentration in the interstitium decreases, and less ADM is able to act on smooth muscle cells to exert its vasodilatory activity. In the progression to septic shock, when it comes to excessive vasodilation and hypotension, administration of ADRECIZUMAB thus can reduce vasodilation by substracting excessive levels of interstitially located ADM.

At the same time levels of ADRECIZUMAB-bound ADM increase in the blood circulation, and it is assumed that this can be functionally relevant: due to its epitope specificity for the N-terminal moiety of ADM, ADRECIZUMAB is a special anti-ADM antibody. While it is a high-affinity antibody, its binding to ADM does not completely block the function of ADM, but rather only partially reduces its capacity to elicit a second messenger response.
The net effect of an increase of ADRECIZUMAB-bound ADM in the blood circulation on the one hand, and an only partial functional inhibition of ADM brought about by the binding of ADRECIZUMAB on the other hand, is that more ADM activity is present in the blood circulation after administration of ADRECIZUMAB than without administration of ADRECIZUMAB. The increased net activity in the blood circulation could promote stabilization of endothelial permeability.

An additional effect of binding of ADRECIZUMAB to ADM in the blood circulation could be an * at least partial and/or temporal * protection from otherwise occurring proteolytic decay of ADM. Proteolytic degradation of ADM occurs at its N-terminus. It is exactly this site, where ADRECIZUMAB binds to ADM.
In accordance with the proposed mode of action, the dosing goal for ADRECIZUMAB is as follows: ADRECIZUMAB in septic shock is intended to be efficacious for at least 7 days after single administration (T/2 ~ 15 days). Therefore, a dose of ADRECIZUMAB should be chosen, which leads to
a) elevation (compared to baseline) of plasma ADM immunoreactivity, as measured by the bio-ADM assay, for up to minimally 7 days, and
b) plasma levels of ADRECIZUMAB for up to minimally 7 days, which are in considerable excess over endogenous ADM.

While an initial increase of plasma ADM immunoreactivity has been observed after administration of a minimal dose of 0.2-0.4 mg/kg (healthy mice; Study No. Safety-06), at least 2 mg/kg were required to achieve an elevation of plasma ADM immunoreactivity over baseline for 7 days after administration of ADRECIZUMAB (Phase Ia Study). With this dose of 2 mg/kg, the concentration of free ADRECIZUMAB was above 10 µg/mL. Similarly, in a CLP mouse model (Study No. CLP-09/3), by using the same dose (2 mg/kg), both plasma ADM immunoreactivity and levels of free ADRECIZUMAB were elevated 7 days after administration of ADRECIZUMAB. Thus, it is concluded that 2 mg/kg ADRECIZUMAB should be chosen as the minimum dose for the planned Phase II study.

Study objective

Patients will be evaluated for safety and tolerability of the therapy, but also for signs of clinical efficacy. As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score as long as arterial line is in place for determination of PaO2/FiO2. Additional blood samples for laboratory analyses will be taken prior to start of IMP infusion (day 1) and within the timeframe of 24 hours (+/- 10 hours) after end of IMP infusion (day 2), 48 hours, 96 hours and 144 hours after the end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from Intensive Care (whatever comes first) for determination of ADM (prior to infusion) and the biomarker MR-proADM and inflammatory biomarkers PCT, IL-6 and penKid.

Primary aim of this phase II study is to demonstrate safety and tolerability as well as efficacy of ADRECIZUMAB in patients with septic shock. The current phase II study is underpowered to detect a relevant reduction of 28-day mortality by ADRECIZUMAB; on the other hand, there is evidence from our animal models that ADRECIZUMAB can improve organ function. The improvement in organ function is measurable using days with relevant organ support (cardiac, renal, respiratory) while on ICU. Therefore, a composite endpoint of days with organ support AND all-cause of mortality will be used: the *Sepsis Support Index* (SSI). Further, it is intended to determine pharmacodynamics and pharmacokinetics of ADRECIZUMAB.

Study design

This is a double-blind, placebo-controlled, dose-finding, multicenter randomized proof of concept phase II study using two doses of ADRECIZUMAB in patients with early septic shock and a bio-ADM plasma concentration at admission of > 70 pg/ml.

Early septic shock is defined as a life-threatening organ dysfunction due to dysregulated host response to a proven or suspected infection which leads to a decline of MAP < 65mm Hg which is refractory to fluid resuscitation and requires vasopressors. Early is defined as a maximum of < 12 hours between onset of the cardiovascular organ-dysfunction (start of vasopressor use) and administration of ADRECIZUMAB. Refractoriness to fluid resuscitation is defined as a lack of response to the administration of 30 ml of fluid per kilogram of body weight or is determined according to a clinician*s assessment of inadequate hemodynamic results.

In this phase II study 300 patients with early septic shock and a plasma concentration of bio-ADM > 70 pg/mL from surgical, medical and mixed ICU at multiple centers in Europe will be randomized. This concept is based on the observation of the clinical observation study AdrenOSS-1, in which 201 out of 291 patients with septic shock and a bio-ADM concentration > 70 pg/mL had a 28-day mortality rate of approximately 35% compared with 84 out of 291 patients with a bio-ADM concentration < 70 pg/mL who had a 28-day mortality rate of 23 %.

All patients will be treated according to *International Guidelines for Management of Severe Sepsis and Septic Shock*.
300 patients with early septic shock will be randomized into two treatment arms and one control group. After informed consent has been signed by patient or legally designated representative and the result from plasma-ADM concentration (> 70 pg/ml) is available, inclusion and exclusion criteria will be checked via a centralized procedure. After fulfilling the inclusion and exclusion criteria patients will be assigned randomly (randomization 1:1:2; four * block randomization per center) to the treatment arms (2 mg/kg or 4 mg/kg) or to the placebo control group.

Patients assigned to the treatment arms will be administered a single dose of ADRECIZUMAB as i.v. infusion over approximately 1 hour; patients assigned to the control group will be administered placebo as i.v. infusion over approximately 1 hour.

Patients will be evaluated for safety and tolerability of the therapy, but also for signs of clinical efficacy. As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score as long as arterial line is in place for determination of PaO2/FiO2.
Additional blood samples will be taken prior to start of IMP infusion (day 1) and within the timeframe of 24 hours (+/- 10 hours) after end of IMP infusion (day 2), at 48 hours, 96 hours and 144 hours after the end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from Intensive Care (whatever comes first) for determination of ADM (prior to infusion) and the biomarker MR-proADM and inflammatory biomarkers PCT, IL-6 and penKid.

Patient accrual is expected to be completed within 24 months.

An interim analysis is planned after 50% of patients (n= 150) have completed the study after day 28.

Intervention

All patients will be treated according to *International Guidelines for Management of Severe Sepsis and Septic Shock*.

Eligible patients (confirmed by central verification) will be randomized (1:1:2) to ADRECIZUMAB treatment arm A
(2 mg/kg) or to ADRECIZUMAB treatment arm B (4 mg/kg) or to placebo as control group. Patients assigned to the treatment arm A or B will be administered a single dose of ADRECIZUMAB as intravenous infusion over approximately 1 hour; patients assigned to the control group will be administered placebo as intravenous infusion over approximately 1 hour.

As long as the patients are on the ICU, daily measurements of clinical signs

and laboratory data will be collected for safety reasons and for determination of SOFA score. Additional blood samples for central laboratory analyses will be taken prior to start of IMP infusion (day 1) and 24 hours, 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU (whatever comes first) after the end of infusion for measurement of biomarkers.

The SOFA score and its components will be determined for all patients over the entire stay on the ICU (28 days or until discharge whatever comes first). Two preconditions need to be fulfilled for this: Daily measurement of platelets and daily assessment of blood gas analysis (BGA) from arterial blood. Safety monitoring for each patient will begin at the time of signing the Informed Consent Form and continue for 90 days after end of short-term infusion of study medication.

At selected study centers a PK substudy will be performed to determine the profile of ADRECIZUMAB in 80 randomized patients.

Study burden and risks

Study procedures are scheduled for screening, administration of study medication and for assessment of the safety and tolerability of the investigational treatment, as well as until the end of the study as outlined in the flow-chart (Protocol p 14 Figure 1, page 16 Figure 2, and page 17 Figure 3).
The procedures on particular study days are described in more detail as from page 40 onwards.

As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score as long as arterial line is in place for determination of PaO2/FiO2. Additional blood samples for central laboratory analyses will be taken prior to start of IMP infusion (day 1) and within the time frame of 24 hours (+/- 10 hours) after end of IMP infusion (day 2). Further timepoints for blood sampling will follow at 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU (whatever comes first) for determination of ADRECIZUMAB, inflammatory biomarker and cardiac biomarkers.
The SOFA score and its components will be determined daily for all patients over the entire stay on the ICU until day 28 or discharge (whatever comes first). Safety monitoring for each patient will begin at the time of signing the Informed Consent Form and continue for 90 days after end of short-term infusion of study medication.

Blood samples will be taken for determination of the following biomarkers prior to start of IMP infusion (day 1) and within the timeframe of 24 hours (+/- 10

hours) after end of IMP infusion (day 2), as well as at 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from ICU (whatever comes first): bio-ADM, MR-pro-ADM, inflammatory biomarkers PCT, IL-6 and penKid.
EDTA blood, 2 samples of 7 ml content (resulting in approximately half the volume of plasma) are collected at each time point.

At selected study centers a PK substudy will be performed to determine the profile of ADRECIZUMAB in 80 randomized patients.
Blood samples (2 ml EDTA blood at each time point) will be obtained prior to ADRECIZUMAB dosing and after 30 minutes as well as 24 hours, 48 hours, 96 hours, 144 hours and 648 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU (whatever comes first) (during stay in ICU or on day 28 follow-up, if patient is discharged from ICU prior to day 28).

No patient diaries will need to be completed.

Euro-QoL * 5 Quality of Life Short Form will be completed at the day of discharge from ICU (day 2 to day 28 or discharge, whatever comes first), and on follow-up day 28. patients will be called from the investigator's site on follow-up day 90 after end of infusion of study medication for completion of the paper telephone Euro-Qol - 5 Quality of Life Short Form.

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. Written informed consent by patient or legally designated representative (according to country * specific regulations)
2. Male and female patient, age * 18 years
3. Body weight 50 kg * 120 kg
4. Bio-ADM concentration > 70 pg/ml
5. Patient with early septic shock (start of vasopressor therapy < 12 hours)
6. Women of childbearing potential must have a negative pregnancy serum or urine pregnancy test before randomization
7. Highly effective method of contraception must be maintained for 6 months after study start by women of childbearing potential and sexually active men.
8. No care limitation

Exclusion criteria

1. Moribund
2. Pre-existing unstable condition (e.g. a recent cerebral hemorrhage or infarct, a recent acute unstable myocardial infarction (all < 3 months), congestive heart failure * NYHA Class IV)
3. Patients that required cardiopulmonary resuscitation in the last 4 weeks prior to evaluation for enrollment
4. Severe COPD with chronic oxygen need at home (GOLD IV)
5. Any organ or bone marrow transplant within the past 24 weeks
6. Uncontrolled serious hemorrhage (* 2 units of blood / platelets in the previous 24 hrs.). Patients may be considered for enrollment if bleeding has stopped and patient is otherwise qualified
7. Uncontrolled hematological / oncological malignancies
8. Absolute neutropenia < 500 per *L
9. Severe chronic liver disease (Child-Pugh C)
10. Systemic fungal infection or active tuberculosis
11. Neuromuscular disorders that impact breathing / spontaneous ventilation
12. Burns > 30% of body surface

13. Plasmapheresis
14. Breastfeeding women
15. Participation in a clinical trial involving another investigational drug within 4 weeks prior to inclusion
16. Unwilling or unable to be fully evaluated for all follow-up visits

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):	27-03-2018
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	HAM8101
Generic name:	Adrecizumab

Ethics review

Approved WMO

Date:	24-08-2017
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2019
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	EUCTR2016-003883-38-NL
ClinicalTrials.gov	NCT03085758
CCMO	NL61059.091.17