A randomized double-blind placebo-controlled phase 1 study regarding safety, tolerability and pharmacokinetics/-dynamics of escalating single intravenous doses of ADRECIZUMAB (HAM 8101) in healthy male subjects.

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To assess the safety, tolerability and pharmacokinetic/-dynamic response, of single escalating doses of ADRECIZUMAB (0.5 mg/kg, 2mg/kg and 8 mg/kg administered as single infusion over 1 hour) in healthy male subjects.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON43493

Source
ToetsingOnline

Brief title
ADRECIZUMAB-phase1

Condition

- Bacterial infectious disorders

Synonym
Sepsis, severe bacterial infection.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ADRECIZUMAB, Adrenomedullin, Healthy volunteers, Phase I

Outcome measures

Primary outcome

Adverse events

Vital signs during the first 8 hours after administration of ADRECIZUMAB:

- Heart rate (continuously by ECG leads)

- Blood pressure (continuously by intra-arterial line)

- Oxygen saturation (continuously by pulse-oximetry)

- Temperature (measured intermittently in the ear by infrared thermometer)

Local tolerability at site of i.v. infusion

Safety laboratory parameters:

- Hb, Ht, leucocytes, thrombocytes, leucocyte differential blood count,

sodium, potassium, creatinine, urea, alkaline phosphatase, ALT, AST, *GT, CK,

PCT, CRP.

-12-lead electrocardiogram (ECG), at baseline, within 1 hour after

ADRECIZUMAB administration, and at 7 to 8 hrs after ADRECIZUMAB administration.

Secondary outcome

* Pharmacokinetics of ADRECIZUMAB: AUC, Cmax, terminal t1/2, Cl, V.

* Blood plasma levels of adrenomedullin

* Ex vivo cytokine production (whole blood will be stimulated with LPS after

which cytokine production will be determined by ELISA).

Study description

Background summary

Adrenomedullin (ADM) is a natural occurring 52 amino acid peptide which is mainly expressed in endothelial and smooth muscle cells. It is enhanced in patients with sepsis, the plasma level of ADM increases with severity of disease. ADM is a key regulator of endothelial integrity in sepsis. It affects blood pressure positively in septic patients via restoring vascular integrity.
In a septic rat model the administration of Adrenomedullin ADM led to a reduction of endothelial hyperpermeability, improvement of blood pressure and improvement of cardiac index, and increased survival.
ADRECIZUMAB is an antibody against the N-terminus of ADM which inhibits the ADM function for approximately 20%. If administered to healthy animals the total ADM plasma level (all ADM is bound to the ADRECIZUMAB) increases immediately (< 15min) and dose-dependently (to 3 * 4 *fold higher level at intended therapeutic dose of 2 mg/kg) and declines according to the t1/2 of IgG antibodies. Combined with the only partial inhibition by the antibody, this means, the overall active ADM level is significantly increased. The immediate increase of total ADM could also be observed in a porcine-two hit model of septic endotoxemia. The fast increase of total ADM led to an improved renal function (creatinine clearance) and reduced inflammation (IL-6) 12 h after administration of ADRECIZUMAB. Similar observations were described in a resuscitated mouse CLP-model after cecal ligation and puncture (CLP). Administration of ADRECIZUMAB led to an improvement of sepsis haemodynamics (reduced catecholamine demand to maintain blood pressure), increase of creatinine clearance and better fluid balance. The CLP-induced kidney barrier dysfunction expressed by extravascular albumin accumulation was significantly protected.
The administration of ADRECIZUMAB to rodents and non-human primates (NHP) has been tolerated very well. Single dose administration up to 800 mg/kg ADRECIZUMAB to rats and 100 mg/kg/day to non-human primates have not shown any clinical side-effects orand no histopathological findings. Even the administrations of 400 mg/kg/day over 14 days to rats and 100 mg/kg over 14 days to NHP in the regulatory pre-clinical toxicology and safety study have not shown any clinical side-effects or histopathological findings. No effect on blood pressure was observed in healthy conscious telemetered beagle dogs when up to 50 mg/kg ADRECIZUMAB was administered.
Based on these data the NOAEL (none-observed adverse events level) in NHP is 100 mg/kg (max. tested) and the NOAEL in rats is 400 mg/kg (max. tested). Based

on these findings the starting dose for human beings should be 0.5 mg/kg ADRECIZUMAB as single infusion over 1 hour and should be increased up to 8 mg/kg. The main reasoning for the dose selection is to have a sufficient safety margin for the intended therapeutic dose of 2 mg/kg. As the actual body weight might be hard to acquire in critically ill patients, and a slightly higher dose for a later treatment may turn out be more beneficial, 8 mg/kg gives a sufficient safety window.

Prior to use the ADRECIZUMAB during experimental human endotoxemia and in septic patients, we wish to test ADRECIZUMAB under non-inflammatory conditions when the ADM system is not activated. Therefore, if ADRECIZUMAB alone is well tolerated in healthy male subjects, it is intended to investigate the safety, tolerability and pharmacokinetics/-dynamics of ADRECIZUMAB in healthy male subjects during experimental LPS-induced endotoxemia, as ADM concentrations are increased during experimental human endotoxemia. The protocol for this ADM-endotoxemia trial will be submitted when the current phase 1 trial is conducted.

Study objective

To assess the safety, tolerability and pharmacokinetic/-dynamic response, of single escalating doses of ADRECIZUMAB (0.5 mg/kg, 2mg/kg and 8 mg/kg administered as single infusion over 1 hour) in healthy male subjects.

Study design

Randomized, double-blind, placebo-controlled, phase 1 study with single escalating doses of ADRECIZUMAB administered as intravenous (i.v.) infusion in 3 sequential group (1st group 0,5 mg/kg, 2nd group 2mg/kg, 3rd group 8 mg/kg) of healthy male subjects. (n=6 active, n = 2 placebo for each group).

Intervention

Single escalating doses of ADRECIZUMAB, administered as intravenous (i.v.) infusion in 3 treatment groups with sequential higher doses (0.5 mg/kg, 2mg/kg and 8mg/kg) and 1 treatment group with placebo administration.

Subjects from the 4 treatment groups are divided over 3 groups of 8 subjects:
Group 1: 0.5 mg/kg (n=6) + placebo (n=2) by 1-hour infusion.
Group 2: 2 mg/kg (n=6) + placebo (n=2) by 1-hour infusion.
Group 3: 8 mg/kg (n=6) + placebo (n=2) by 1-hour infusion.

The first 4 subjects of each dosage group will be treated on consecutively.

Adrecizumab summary:
0.5 mg/kg or 2mg/kg or 8 mg/kg ADRECIZUMAB dissolved in NaCl 0.9%.

* Recombinant monoclonal antibody from Chinese hamster ovary (CHO) cells
* High level of *humanization* (92%)
* IgG1 kAPPA
* Binding epitope: N-terminus of ADM
* Concentration: 20 mg/mL
* Vehicle: 20 mM His/HCl, 300 mM Glycin, pH 6.0
* Dilution solution: 0.9% NaCl
* Stability (interim): 12 months at +2 - +8°C

Study burden and risks

Blood withdrawal during the study is restricted to a smaller volume than is withdrawn during routine phlebotomy at the blood bank, and is not associated with relevant risks. Venipunctures and, vascular and arterial cannulation at the several study visits carries the risk of hematoma at the puncture sites, which will spontaneously resolve, should they occur. Blood loss from puncture sites after removal of cannulas will be stopped by applying pressure. A pressure bandage will be applied to the site of arterial cannulation. Also, vasovagal reactions can occur during a puncture procedure, which can be adequately treated.

The administration of ADRECIZUMAB to rodents and non-human primates has been tolerated very well. Single dose administration up to 800 mg/kg ADRECIZUMAB to rats and 100 mg/kg to NHP have not shown any clinical adverse effects and no histopathological findings. Even the administrations of 400 mg/kg over 14 days to rats and 100 mg/kg over 14 days to NHP within the regulatory pre-clinical toxicity and safety study have not shown any clinical or histopathological findings. No effect on blood pressure could be observed in healthy conscious telemetered beagle dogs when up to 50 mg/ kg ADRECIZUMAB were administered.

In our opinion, the estimated risks for participation in this study are low, and we have made every effort to minimize risks or counteract potential adverse reactions. The slow infusion rate ofd ADRECIZUMAB and LPS (infusion in hours) enables us to stop the infusion at any time during administration after which side effects will most likely rapidly decline. Hospitalization of the subjects for 8 hours after administration of ADRECIZUMAB will enable us to react immediately and professionally in case unexpected adverse events would occur. According to the NFU-criteria, the risks of this study are negligible. As a extra safety measure, we have created a Data Safety Management Board, that will do interim analysis of the study.

We feel that the remaining risks are acceptable and do not outweigh the scientific and medical relevance of this study

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 to participate in this trial prior to any study mandated procedure.
2. Male subjects aged 18 to 35 years, inclusive.
3. Subjects have to agree to use a reliable way of contraception with their partners from study entry until 3 months after study drug administration.
4. BMI between 18 and 30 kg/m², with a lower limit of body weight of 50 kg and a upper limit of 100 kg.
5. Healthy as determined by medical history, physical examination, vital signs, 12 lead electrocardiogram, and clinical laboratory parameters

Exclusion criteria

1. Unwillingness to abstain from any medication, recreational drugs, anti-oxidant or vitamin supplements during the course of the study and within 7 days prior to the treatment day.
2. Unwillingness to abstain from smoking or alcohol 1 day prior to the treatment day and during the first 24 hours of the study.
3. Surgery or trauma with significant blood loss or blood donation within 3 months prior to the treatment day.
4. History, signs or symptoms of cardiovascular disease, in particular:
* History of frequent vasovagal collapse or of orthostatic hypotension
* Resting pulse rate *45 or *100 beats / min
* Hypertension (RR systolic >160 or RR diastolic >90)
* Hypotension (RR systolic <100 or RR diastolic <50)
* Conduction abnormalities on the ECG consisting of a 1st degree atrioventricular block or a complex bundle branch block
* Any chronic cardiac arrhythmias, except PAC*s, PVC*s
5. Renal impairment: plasma creatinine >120 µmol/L
6. Liver function tests (alkaline phosphatase, AST, ALT and/or *-GT) above 2x the upper limit of normal.
7. History of asthma
8. Atopic constitution
9. CRP above 2x the upper limit of normal or clinically significant acute illness, including infections, within 2 weeks before administration of the study drug.
10. Treatment with investigational drugs or participation in any other clinical trial within 30 days prior to study drug administration.
11. Known or suspected of not being able to comply with the trial protocol.
12. Known hypersensitivity to any excipients of the drug formulations used.
13. Inability to personally provide written informed consent (e.g. for linguistic or mental reasons) and/or take part in the study.

Study design

Design

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):	23-05-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-01-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-12-2016
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	EUCTR2015□005671□24-NL
CCMO	NL56312.091.16

Study results

Date completed:	22-09-2016
Actual enrolment:	24