A randomized double-blind placebo-controlled phase I study on the safety, tolerability and pharmacokinetics/-dynamics of escalating single intravenous doses of ADRECIZUMAB (HAM8101) in healthy male subjects during experimental endotoxemia.

Published: 30-08-2016
Last updated: 14-04-2024

Primary Objective:1. To assess the safety and tolerability of single escalating doses of Adrecizumab in healthy male volunteers during experimental endotoxemia.Secondary Objectives:2. To determine the pharmacokinetics of single escalating doses of...

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

Summary

ID

NL-OMON43006

Source
ToetsingOnline

Brief title
Adrecizumab-LPS

Condition

- Other condition
- Hepatobiliary neoplasms malignant and unspecified

Synonym

Sepsis

Health condition

Experimentele endotoxemie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Adrecizumab, Adrenomedullin, LPS

Outcome measures

Primary outcome

The primary study endpoint is safety, consisting of:

- Adverse Events

- Vital signs during the first 8 hours after Adrecizumab administration and at

follow-up periods (T=24 hours, T=7 days, T=14 days, T=28 days, T=60 days, T=90

days):

o Heart rate

o Blood pressure

o Oxygen saturation

o Temperature

- Local tolerability at site of i.v. infusion.

- Safety laboratory parameters

o Hb, Ht, leukocytes, thrombocytes, leukocyte differential blood count, sodium,

potassium, creatinine, urea, alkaline phosphatase, ALT, AST, GGT, CK, CRP, PT,

APTT.

- 12-lead electrocardiogram (ECG), 2 and 8 hours after Adrecizumab

administration.

Secondary outcome

- Pharmacokinetics of Adrecizumab during experimental endotoxemia (AUC, Cmax,

Terminal T1/2, Cl, V)

- Pharmacodynamics (blood plasma levels of Adrenomedullin) during experimental

endotoxemia.

- Plasma levels of inflammatory mediators on the endotoxemia day (including but

not limited to TNFα, IL-6, IL-8, IL-10, IL-1RA).

- Symptom score.

- Kidney damage markers (including but not limited to pro-enkephalin,

creatinine clearance, NGAL, KIM-1)

Study description

Background summary

Adrenomedullin (ADM) is a natural occurring 52 amino acid peptide which is mainly expressed in endothelial and smooth muscle cells. Plasma levels of ADM are increased in patients with sepsis, SIRS and after surgery, and are associated with short-term mortality and vasopressor requirement. Although the correlation of higher ADM concentrations with impaired outcome might suggest that ADM is deleterious, this is not necessarily the case, as is shown by several preclinical studies both in vitro as in vivo.

Adrecizumab is a monoclonal antibody against the N-terminus of ADM which inhibits the ADM function by approximately 20%. Compared to other antibodies, Adrecizumab gives the least inhibition of ADM and also improves survival in septic animals most pronounced. Administration of Adrecizumab in healthy animals increases the total ADM plasma immediately and dose-dependently and declines according to the t1/2 of IgG antibodies. Combined with the only

partial inhibition by the antibody, this means that the overall active ADM level is significantly increased.

Preclinical studies have shown that Adrecizumab administration in a wide variety of animal models of septic shock led to improved outcome: Improved hemodynamic parameters, reduced edema, reduced catecholamine requirement, reduced inflammation and ultimately improved survival.

Preclinical toxicology studies with single and repeated administrations of Adrecizumab to rodents, dogs and non human primates (NHP) were tolerated very well and showed no clinical or histopathological findings.

The safety and tolerability of Adrecizumab administration in humans was recently investigated under *baseline circumstances* (no inflammation or activation of the ADM system) in the Adrecizumab-phase 1 study (CMO 2016-2283). In this randomized, double-blinded, placebo-controlled phase 1 study, 24 healthy male volunteers were recruited and randomized to receive either Adrecizumab or placebo. Four groups (n=6 each) received study drug by i.v. infusion over a 1 hour period (either Adrecizumab 0.5 mg/kg, 2.0 mg/kg, 8.0mg/kg or placebo). The subjects were admitted to the research unit of the department of Intensive Care of the Radboudumc for the first 8 hours after study drug administration for continuous monitoring, electrocardiographic investigations and blood withdrawal. The 3 month follow-up period of this study is still ongoing but an interim 14 day safety/tolerability report showed no indications of any unfavorable effects of Adrecizumab, meaning no SAEs occurred, there were no signs of local intolerability at the site of i.v. infusion and there were no serious alterations or abnormalities in vital signs, ECGs and safety laboratory parameters (see Adrecizumab-phase1 14 day safety/tolerability report, a separate document for this Ethics Committee submission).

Prior to investigating Adrecizumab efficacy in septic patients, we wish to assess the safety, tolerability and pharmacokinetics/-dynamics of Adrecizumab under inflammatory conditions in healthy volunteers. The experimental human endotoxemia model, in which healthy male volunteers receive a low dose of lipopolysaccharide (LPS) derived from Escherichia coli, is widely used to study the effects of systemic inflammation in humans in vivo and is considered a safe and highly reproducible method to activate the innate immune system.14 Furthermore, previous data has shown that experimental human endotoxemia results in increased plasma ADM levels (see Figure 1).

Study proposal: We propose a randomized double-blind, placebo-controlled study in 24 healthy male volunteers who will be given single, escalating per group doses of Adrecizumab during experimental human endotoxemia in which ADM plasma concentrations are elevated. A similar study design and similar doses of Adrecizumab (0.5, 2.0 and 8.0 mg/kg) will be used as in the previous

Adrecizumab phase I study.

Study objective

Primary Objective:
1. To assess the safety and tolerability of single escalating doses of Adrecizumab in healthy male volunteers during experimental endotoxemia.
Secondary Objectives:
2. To determine the pharmacokinetics of single escalating doses of Adrecizumab during experimental endotoxemia.
3. To determine the effects of Adrecizumab on Adrenomedullin concentrations (pharmacodynamics) during experimental endotoxemia.
4. To determine whether Adrecizumab modulates the absolute plasma cytokine levels upon experimental endotoxemia.
5. To determine the effects of Adrecizumab on LPS-induced clinical symptoms (illness score) as well as hemodynamic and temperature changes.
6. To determine the effects of Adrecizumab on LPS-induced markers of kidney damage.

Study design

A randomized, double-blind, placebo-controlled phase I study in healthy male volunteers during experimental endotoxemia with single, escalating per group doses of Adrecizumab administered as i.v. infusion over a 1 hour period. A continuous LPS (lipopolysaccharide) model is used to induce experimental endotoxemia; administration of LPS in an initial bolus of 1 ng/kg followed by continuous infusion at 1 ng/kg/hr for 3 hours. Subject will receive one course of treatment with study medication (Adrecizumab or placebo), 1 hour after start of LPS administration.

Intervention

- All subjects will undergo experimental endotoxemia. A continuous LPS (lipopolysaccharide) model will be used to induce experimental endotoxemia; administration of LPS in an initial bolus of 1 ng/kg followed by continuous infusion of 1 ng/kg/hr for 3 hours.
- Single dose of study medication (Adrecizumab 0.5, 2.0, 8.0 mg/kg, or placebo), 1 hours after start of LPS administration.

Study burden and risks

Total time burden for the study is approx. 12.5 hours: 1 hour for screening, 10 hours for the admission day, and six 15-minutes follow-up visits. Volunteers will be recruited and are subject to a medical examination (including interview, medical history, blood withdrawal and physical examination). Blood withdrawal during the study is restricted to a smaller volume (<500 mL) than is

withdrawn during routine phlebotomy at the blood bank, and is not associated with relevant risks. Venipunctures and vascular access at the several study visits carries the risk of hematoma at the puncture sites, which will resolve spontaneously, 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.

Adrecizumab was generated by CDR grafting of a murine IgG and has a composition of 92.5% amino acid sequence of human IgG1. This means that it has a high level of humanization. Antibodies with a high level of humanization are better tolerated by humans then antibodies with a low level of humanization. Also, the administration of Adrecizumab to rodents, 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 repeated administrations (day 1 / 4 / 8 / 14) 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 humans, the safety- and tolerability of Adrecizumab has recently been explored in a phase I study. Single escalating doses of Adrecizumab (up to 8.0 mg/kg) were administered i.v. over a 1 hour period and tolerated well. Although the study is still blinded, it is already known that the administration of a single dose of Adrecizumab to healthy volunteers was associated with NO moderate or serious adverse events and was very well tolerated.

The administration of a lipopolysaccharide (LPS) induces flu-like symptoms. This model of systemic inflammation has been applied for more than 10 years in our department and thousands of subjects worldwide have participated in endotoxemia trials. During the endotoxemia experiment day, subjects will be under constant supervision of a physician with continuous monitoring of blood pressure and heart rate. The endotoxemia protocol and associated risks are identical to earlier endotoxemia studies performed in our institute.

The combination of Adrecizumab and LPS has not been investigated before.

Placing the arterial cannula can hurt, this is why it is placed under local anesthesia.

Time burden: screening (1hr), 1 experimental day, 6 follow-up visists.

Subjects will not benefit directly from participation to the study. The total risks to the subjects in this study is classified as an *intermediate risk* (low risk on minor harms). A subject fee is provided.

Contacts

Public
Adrenomed AG

Neuendorfstr. 15a
Hennigsdorf 16761
DE
Scientific
Adrenomed AG

Neuendorfstr. 15a
Hennigsdorf 16761
DE

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.
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

A potential subject who meets any of the following criteria will be excluded from participation:
1. Unwillingness to abstain from any medication, including recreational drugs 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, within 1 day prior to the treatment day and 1 day after the treatment day.
3. Previous participation in a trial where LPS was administered.
4. Surgery or trauma with significant blood loss or blood donation within 3 months prior to the treatment day.
5. 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 mmHg)
• Hypotension (RR systolic <100 or RR diastolic <50 mmHg)
• 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)
6. Renal impairment: plasma creatinine > 120 µmol/L
7. Liver function tests (alkaline phosphatase, AST, ALT and/or γ-GT) above 2x the upper limit of normal.
8. History of asthma
9. Atopic constitution.
10. CRP above 2x the upper limit of normal, or clinically significant acute illness, including infections, within 2 weeks prior to the treatment day.
11. Treatment with investigational drugs or participation in any other clinical trial within 30 days prior to the treatment day.
12. Known or suspected of not being able to comply with the trial protocol.
13. Known hypersensitivity to any excipients of the drug formulations used.
14. 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):	04-01-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	30-08-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2016
Application type:	First submission
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	EUCTR2016-003218-29-NL
CCMO	NL58811.091.16

Study results

Date completed:	24-05-2017
Actual enrolment:	24