Randomized double blind placebo-controlled clinical safety, tolerability and pharmacokinetic/-dynamic study on the effects of escalating single intravenous doses of EA-230 on the innate immune response during experimental human endotoxemia

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Part 1: To assess the safety, tolerability and pharmacokinetic-dynamic response, of single escalating doses of EA-230 in healthy subjects.Part 2: To assess the dose-and plasma concentration-response relation of single escalating doses EA-230 on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON40791

Source
ToetsingOnline

Brief title
PK/PD of EA-230 during endotoxemia

Condition

- Immune disorders NEC
- Renal disorders (excl nephropathies)

Synonym

inflammatory response

Research involving
Human

Sponsors and support

Primary sponsor: Exponential Biotherapies inc.
Source(s) of monetary or material Support: EBI Anti Sepsis B.V

Intervention

Keyword: Acute Kidney Injury, EA-230, Endotoxemia, Inflammatory response

Outcome measures

Primary outcome

Part 1: Safety and tolerability of EA-230

Part 2: Modulation by EA-230 of the LPS-induced inflammatory response,

quantified by the change in area under the curve (AUC) of the concentration *

time curve of TNF-α during endotoxemia

Secondary outcome

Part 1:

Pharmacokinetics of EA-230

-Blood plasma levels of EA-230 and, if possible, metabolites, AUC, Cmax,

terminal t1/2, Cl, V

-Urinary excretion profile of EA-230 and, if possible, metabolites.

Vital signs

-blood pressure

-heart rate

Adverse events

Safety parameters

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

-Safety laboratory parameters (Hb, Ht, Leucocytes, thrombocytes, Leucocyte differential blood count, sodium, potassium, creatinine, urea, alkaline phosphatase, ALT, AST, γGT, CK, CRP)

-Electrocardiogram (ECG), at baseline, just after IMP administration, and at 7 to 8 hrs after IMP administration

Part 2:

Modulation by EA-230 of the LPS-induced inflammatory response, quantified by the change in AUC of the concentration * time curve of other cytokines during endotoxemia (IL-6 and IL-10)

Modulation by EA-230 of the LPS-induced leucocyte response, quantified by total WBC counts, neutrophil counts and monocyte counts over 24 hours after LPS challenge

Modulation by EA-230 of markers of inflammation-induced kidney injury

-Urinary excretion of NGAL, KIM-1, cystatin C, microalbumin, creatinine and urea

-Plasma concentration of creatinine, urea, and NGAL in plasma

Modulation by EA-230 of inflammation-induced changes in renal function

-Glomerular filtration rate (GFR) measured by the clearance of iohexol

Pharmacokinetics of EA-230

-Blood plasma levels of EA-230 and, if possible, metabolites, AUC, Cmax, terminal t1/2, Cl, V

-Urinary excretion profile of EA-230 and, if possible, metabolites.

Vital signs

-blood pressure

-heart rate

Adverse events

Safety parameters

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

-Safety laboratory parameters (Hb, Ht, Leucocytes, thrombocytes, Leucocyte

differential blood count, sodium, potassium, creatinine, urea, alkaline

phosphatase, ALT, AST, γGT, CK, CRP)

-Electrocardiogram (ECG), at baseline, just after IMP administration, and at 7

to 8 hrs after IMP administration

Study description

Background summary

Although the immune system is essential to survival, a variety of diseases originate from inappropriate activation of the immune response. Besides a range of auto-inflammatory disease like rheumatoid arthritis, inappropriate or undesirable activation of the immune system can occur during infectious diseases like sepsis, after major surgery like cardiac artery bypass grafting, after radiation therapy in the treatment of cancer, or after organ transplantation.
For auto-inflammatory diseases, in the last decades therapies have come available that specifically target parts of the immune system. The development of *biologicals*, recombinant antibodies that specifically block one antigen or receptor, has had an enormous impact on the treatment of chronic autoimmune diseases. However, these treatments have been shown not to be effective in other types of (acute) systemic inflammation, like sepsis.
Of the many downstream consequences of exaggerated inflammatory response, organ injury and failure is the most serious, most often involving the kidneys (Cartin-Ceba et al. 2012,). This also holds true for cardiac surgery with cardiopulmonary bypass, in which various factors, including the inflammatory cascade, cause a temporarily decline or even permanent loss of renal function

(Moss and Lamarche 2012). As kidney failure is an independent prognostic factor for mortality in critically ill patients, treatments aimed at preventing acute kidney injury are warranted.
EA-230 is a novel pharmacological compound being developed for the treatment of systemic inflammatory states like sepsis, and for the treatment of inflammation associated organ dysfunction like acute kidney injury (AKI). It*s a linear tetrapeptide derived from the human chorionic gonadotropin hormone (hCG). It has shown anti-inflammatory properties and protects against organ failure in several pre-clinical models of sepsis or systemic inflammation which will be described in more detail below. Most notably, EA-230 has shown marked protective effects in the kidney during abdominal sepsis in animals. As EA-230 attenuates the pro-inflammatory response in neutrophils and monocytes ex vivo, and neutrophil influx in tissues during systemic inflammation in vivo is abrogated, it is thought that EA-230 acts by protecting the host against the detrimental effects of neutrophils during acute systemic inflammatory diseases, thereby preventing organ damage, especially in the kidney.
Having performed extensive research into the pharmacology, pharmacokinetics and toxicology of EA-230, a first in human study was previously conducted with escalating single doses of EA-230 (NCTxxx) , which showed that EA-230 was well tolerated up to i.v. doses of 30 mg/kg three times a day (daily dose of 90 mg/kg) for three days, and did not result in adverse events that were related to the study treatment. In a human model of systemic inflammation elicited by the administration of a low dose of endotoxin (NCTxxxx), EA-230 showed to attenuate the innate immune response at a single i.v. dose of 10 mg/kg, even though EA-230 was administered 30 minutes after endotoxin administration. A full dose- and concentration-response profile was not collected in that study. In addition, until now, only bolus administrations of EA-230 were tested, whereas in view of the short terminal half life of less than 15 minutes, a continuous administration of EA-230 over a longer time interval may be more effective.
For that reason, an additional phase I study in healthy volunteers is required to complete the profile of EA-230 response in inflammation before a dose or dose range can be chosen for a first *prove-of-concept* study in patients. The safety profile of EA-230 has to be extended beyond the daily dose of 90 mg/kg addressed to date; the dose- and concentration response information collected during escalation will provide the dose for proof-of-concept testing in patients.

Study objective

Part 1: To assess the safety, tolerability and pharmacokinetic-dynamic response, of single escalating doses of EA-230 in healthy subjects.

Part 2: To assess the dose-and plasma concentration-response relation of single escalating doses EA-230 on inflammation and LPS-induced changes in markers for renal function, and to assess safety, tolerability and PK of EA-230 under the

condition of experimental endotoxemia.

Study design

The trial consists of two parts, both with a prospective, monocentric, double-blind, placebo-controlled, randomized, single-dose design in healthy subjects. Part 1 is a phase I trial in which single escalating doses of EA-230 will be administered to healthy volunteers. In part 2, the administration of single escalating doses of EA-230 to healthy volunteers, are combined with the intravenous administration of a low dose of E. Coli endotoxin (also known as lipopoysaccharide or LPS).
A total number of 60 subjects will be examined in the two study parts according to the schedule below. Both study parts are placebo controlled. Placebo treatments are randomly divided over the treatment groups in a double blind fashion.

Study burden and risks

In our opinion, the risks for participation in this study are low, and we have made every effort to minimize risks or counteract potential adverse reactions. EA-230 has been well tolerated in healthy volunteers up to doses of 90 mg/kg*day. In addition, the slow infusion rate (infusion in 2 hours) combined with the short terminal half life of EA-230 enables us to stop the infusion at any time during administration after which side effects will most likely rapidly decline.
We are experienced in handling the potential side effects of LPS administration. Iohexol and PAH administration is regarded safe, with the most likely adverse reaction being an allergic reaction, which we will be capable of managing on our well equipped and staffed research facility. Therefore, 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.Subjects aged 18 to 35 years inclusive, for part 2 only male subjects will be included.
3.Subjects and their partners have to agree to use a reliable way of contraception 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
5.Healthy as determined by medical history, physical examination, vital signs, 12 lead electrocardiogram, and clinical laboratory parameters
6.Negative results for hard drug use from urine drug screen at screening

Exclusion criteria

1.Unwillingness to abstain from any medication, recreational drugs or anti-oxidant vitamin supplements during the course of the study and within 7 days prior to study Day 1.
2.Unwillingness to abstain from nicotine, or alcohol or within 1 day prior to study Day 1
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 studyDay 1
5.History, signs or symptoms of cardiovascular disease, in particular:
• History of frequent vaso-vagal 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

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

Study design

Design

Study type:	Observational invasive
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):	22-01-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	EA-230

Ethics review

Approved WMO

Date:	30-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	07-10-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-02-2015
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	EUCTR2014-002481-78-NL
CCMO	NL49674.091.14

Study results

Date completed:	26-06-2015
Actual enrolment:	60