# Randomized double blind placebo controlled PK/PD study on the effects of a single intravenous dose of NOX-H94 on serum iron during experimental human endotoxemia

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Primary Objective•To assess the pharmacodynamic response after single dose administration of NOX H94 in healthy subjects during experimental endotoxemia.Secondary Objective• To determine the pharmacodynamic effects of NOX H94 after single dose...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Anaemias nonhaemolytic and marrow depression |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35593

**Source**
ToetsingOnline

**Brief title**
PK/PD of NOX-H94 in endotoxemia

### Condition

- Anaemias nonhaemolytic and marrow depression
- Autoimmune disorders
- Ancillary infectious topics

**Synonym**
Anemia of Chronic disease, inflammation associated anemia

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** NOXXON Pharma AG
**Source(s) of monetary or material Support:** ZonMW,NOXXON Pharma AG

## Intervention

**Keyword:** hepcidin, inflammation, iron, NOX-H94

## Outcome measures

### Primary outcome

Primary endpoint

• Change in serum iron concentration at 9 hours after LPS administration versus baseline; comparison of subjects treated with NOX H94 versus placebo.

### Secondary outcome

Secondary endpoints

• Change in serum iron concentrations at 6 and 12 hours after LPS administration versus baseline

• Concentrations of serum iron and of markers of iron homeostasis up to 48 h after LPS injection: serum iron, transferrin saturation (TSAT), ferritin, reticulocyte hemoglobin content (CHR), hemoglobin (Hb), mean cell volume (MCV), mean cell hemoglobin (MCH): AUC of serum iron concentrations, ANOVA of repeat measures of all data points

• Concentration of hepcidin up to 1 week after LPS injection

• Concentrations of pro-inflammatory and anti-inflammatory cytokines up to 48 h after LPS injection: TNF α, IL 6, IL 1RA, IL 10 to document the inflammatory

reaction

• Pharmacokinetic profile of NOX H94

• Safety and tolerability

# Study description

### Background summary

The purpose of this study is to assess the effect of the hepcidin specific antagonist NOX-H94 on the innate immune response and the subsequent changes in hepcidin and iron hemostasis during systemic inflammation induced by experimental human endotoxemia.
In the human endotoxemia model, intravenously administered lipopolysaccharide (LPS) elicits an inflammatory response with release of pro-inflammatory cytokines, such as IL06 and TNF-alfa, with subsequent induction of hepcidin.
As a consequence of hepcidin induction, serum iron concentrations decrease.
Thus, LPS induced human endotoxemia represents a model for a pathophysiological process underlying anemia of inflammation which is characterized by high circulating hepcidin concentrations leading to iron restriction and ineffective erythropoiesis.
This study in healthy subjects investigates the capacity of NOX H94 to inactivate hepcidin and to prevent serum iron decrease in a pathophysiological model prior to studying the efficacy of NOX H94 in patients with anemia with a background of malignancy, inflammation, or chronic kidney disease.

### Study objective

Primary Objective
•To assess the pharmacodynamic response after single dose administration of NOX H94 in healthy subjects during experimental endotoxemia.

Secondary Objective
• To determine the pharmacodynamic effects of NOX H94 after single dose administration in healthy subjects during experimental endotoxemia in relation to its pharmacokinetics.
• To assess the effect of a single dose administration of NOX H94 on the innate immune response during experimental endotoxemia.
• To determine the safety of NOX H94 after single dose administration in healthy subjects during experimental endotoxemia.

### Study design

Randomized double blind placebo controlled intervention study in healthy human volunteers during experimental endotoxemia.

**Intervention**

The volunteers will be randomized to 2 intervention groups.

Group 1. NOX-H94 (N=12):
T= 0: 2ng/kg LPS i.v.
T=0.5 hrs: NOX-H94 1.2 mg/kg i.v.

Group 2. Placebo (N=12):
T= 0: 2ng/kg LPS i.v.
T= 0.5 hrs: Placebo i.v.

Before any intervention pre-hydration will be performed by infusion of 1.5 L 2.5% glucose/0.45% saline solution in approximately 45 minutes, to ensure optimal hydration status. Thereafter LPS derived from E coli O:113 will be injected (2 ng/kg iv., infusion rate: 1 minute). At 30 minutes after LPS infusion NOX-H94 is administered intravenously.

**Study burden and risks**

• Endotoxin infusion is accompanied by flu-like symptoms such as temperature increase (possibly chills), headache, muscleache, backache, loss of appetite and sometimes nausea. Endotoxin can increase also the heart rate and slightly lower the blood pressure. These symptoms normalise within hours.

• NOX-H94 was accompanied by mild side effects in a previous trial, like headache and tiredness. When higher dosages (i.e. 2 and 4 times higher than used in the present study) of the Study drug were administered a temporary mild elevation of liver enzymes was seen. This was only a very mild rise that was completely reversible.

• A catheter is inserted in the artery of the wrist for blood sampling and monitoring. This induces a small chance of a hematoma.

• The amount of blood taken during the study is up to 450 ml per experiment.

• There are no data available yet about the effect of NOX H94 on sperm or its production in the body or about effects on the development of the foetus. Therefore the subjects have to agree to use an effective contraceptive measure for 2 months after study drug administration.

The subjects will not benefit directly from participation in the study. A subject fee is to be provided.

# 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
2. Male subjects aged 18 to 35 years inclusive
3. Subjects and their female partners have to agree to use a reliable way of contraception from screening until 2 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. Serum iron and red blood parameters Hb, MCV, ferritin, serum iron, and total iron binding capacity within reference range

### Exclusion criteria

1. Use of any medication, recreational drugs or anti-oxidant vitamin supplements within 7 days prior to profiling day
2. Use of caffeine, nicotine, or alcohol or within 1 day prior to profiling 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 profiling day
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 γ-GT) outside of the reference range or total bilirubin >20 µmol/L
8. Hemoglobin or iron parameters (iron, transferrin saturation, ferritin) outside of the reference ranges
9. History of asthma
10. Immuno-deficiency
11. Positive test of HIV type 1/2 antibodies, HBs antigen, HBc antibodies and HCV antibodies unless antibody titer is induced by vaccination
12. CRP > reference range or clinically significant acute illness, including infections, within 2 weeks before profiling day of study drug.
13. Treatment with investigational drugs or participation in any other clinical trial within 30 days prior to study drug administration
14. Known or suspected of not being able to comply with the trial protocol.
15. Inability to personally provide written informed consent (e.g. for linguistic or mental reasons) and/or take part in the study.

## Study design

### Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |

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| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 10-01-2012 |
| Enrollment: | 24 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | NOX-H94 |
| Generic name: | NOX-H94 |

## Ethics review

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| Approved WMO Date: | 13-12-2011 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 24-01-2012 |
| 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 | EUCTR2011-005022-22-NL |
| ClinicalTrials.gov | NCTnummervolgt |
| CCMO | NL38191.091.11 |