



## Clinical trial results:

### Effects of oxygen status on endotoxemia induced inflammation and Hypoxia Inducible Factor 1-a. A pilot proof of principle study.

#### Summary

EudraCT number	2013-002390-21
Trial protocol	NL
Global end of trial date	26 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021
Summary attachment (see zip file)	Short-Term Hypoxia Dampens Inflammation in vivo via Enhanced Adenosine Release and Adenosine 2B Receptor Stimulation (PIIS2352396418302287.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	Oxygen_Inflammation
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	Geert Grooteplein 10, Nijmegen, Netherlands, 6500 HB
Public contact	Dorien Kiers, Radboud University Nijmegen Medical Centre, h.kiers@ic.umcn.nl
Scientific contact	Dorien Kiers, Radboud University Nijmegen Medical Centre, h.kiers@ic.umcn.nl

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2013
Global end of trial reached?	Yes
Global end of trial date	26 November 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the effects of hyperoxia and hypoxia compared to normoxia in the human endotoxemia model on kinetics of plasma TNF alpha in healthy volunteers

Protection of trial subjects:

All subjects will visit the hospital for a screening visit in which a medical interview and physical examination will be carried out (30 minutes). At the screening visit and the day after the experiment blood will be obtained by venapuncture. During the experimental day, subjects will receive an arterial line, placed under local anaesthesia. Furthermore, a venous cannula will be placed for the administration of fluids and LPS. The administration of LPS induced flu-like symptoms for approximately 4-6 hrs. This model of systemic inflammation has been applied for many years in thousands of subjects in various research centres in the world. LPS administration is considered safe and no long-term effects have ever been documented. At the Radboud University Medical Centre, over 280 volunteers have received more than 350 injection of LPS. Therefore, there is sufficient experience with this model at this centre. The subjects will be exposed to hypoxia, hyperoxia or normoxia in the ventilation helmet for 3.5 hours, and will be monitored for 5.5 hour after cessation of hypoxia or hyperoxia. There is a large body of scientific work with induction of hypoxia in healthy human subjects; minor side effects as nausea, headache and light-headedness have been reported after six hours of hypoxia, making the chance of these side effects occurring in the present study (3.5 hours of hypoxia) very low. There are no reports of damage, discomfort or other unwanted side-effects of exposure to hyperoxia. The subjects will wear a respiratory helmet that is approved for regular patient care.

A physician or nurse will be present in the experiment room at all times, and subjects will be continuously monitored (heart rate, blood pressure saturation). In total, approximately 350 ml blood will be drawn during the study, which is comparable to previous experiments, and has never resulted in adverse events. Subjects will not benefit directly from participation to the study. A subject fee is provided

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

After approval from the local ethics committee of the Radboud University Medical Center, thirty healthy, male volunteers gave written informed consent to participate in the experiments

### Pre-assignment

Screening details:

Subjects with normal physical examination, electrocardiography, and routine laboratory. Exclusion criteria; febrile illness during 2 weeks before experiment, high altitude exposure in 3 months prior to experiment, use of prescription drugs, history of spontaneous vagal collapse, and participation in previous trial with endotoxin administration.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	hypoxia

Arm description:

subjects were exposed to hypoxia for 3.5 h by titration of FiO<sub>2</sub> to a peripheral saturation (SaO<sub>2</sub>) of 80–85%, using an nitrogen/medical air mixture and an air-tight respiratory helmet (CaStar, StarMed, Italy).

Arm type	Experimental
Investigational medicinal product name	Lipopolysaccharide
Investigational medicinal product code	
Other name	Purified LPS from Escherischa coli (O:113)
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

LPS is used to elicit an inflammatory response in all subjects

Arm title	normoxia
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Arm description:

medical air, FiO<sub>2</sub> of 21%, also using the respiratory helmet and the same airflow rate as in hypoxic subjects,

Arm type	Active comparator
Investigational medicinal product name	Lipopolysaccharide
Investigational medicinal product code	
Other name	Purified LPS from Escherischa coli (O:113)
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

LPS is used to elicit an inflammatory response in all subjects

Arm title	Hyperoxia
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Arm description:

Subjects will be breathing 100% of oxygen

Arm type	Experimental
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Investigational medicinal product name	Lipopolysaccharide
Investigational medicinal product code	
Other name	Purified LPS from Escherischa coli (O:113)
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

LPS is used to elicit an inflammatory response in all subjects

<b>Number of subjects in period 1</b>	hypoxia	normoxia	Hyperoxia
Started	10	10	10
Completed	10	10	10

## Baseline characteristics

### Reporting groups

Reporting group title	hypoxia
Reporting group description: subjects were exposed to hypoxia for 3.5 h by titration of FiO2 to a peripheral saturation (SaO2) of 80–85%, using an nitrogen/medical air mixture and an air-tight respiratory helmet (CaStar, StarMed, Italy).	
Reporting group title	normoxia
Reporting group description: medical air, FiO2 of 21%, also using the respiratory helmet and the same airflow rate as in hypoxic subjects,	
Reporting group title	Hyperoxia
Reporting group description: Subjects will be breathing 100% of oxygen	

Reporting group values	hypoxia	normoxia	Hyperoxia
Number of subjects	10	10	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	10	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	10	10	10

Reporting group values	Total		
Number of subjects	30		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	30		
From 65-84 years	0		

85 years and over	0		
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Gender categorical			
Units: Subjects			
Female	0		
Male	30		

## End points

### End points reporting groups

Reporting group title	hypoxia
Reporting group description: subjects were exposed to hypoxia for 3.5 h by titration of FiO <sub>2</sub> to a peripheral saturation (SaO <sub>2</sub> ) of 80–85%, using an nitrogen/medical air mixture and an air-tight respiratory helmet (CaStar, StarMed, Italy).	
Reporting group title	normoxia
Reporting group description: medical air, FiO <sub>2</sub> of 21%, also using the respiratory helmet and the same airflow rate as in hypoxic subjects,	
Reporting group title	Hyperoxia
Reporting group description: Subjects will be breathing 100% of oxygen	

### Primary: Plasma TNF-alpha concentration following LPS administration

End point title	Plasma TNF-alpha concentration following LPS administration
End point description:	
End point type	Primary
End point timeframe: 1 day	

End point values	hypoxia	normoxia	Hyperoxia	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/ml				
geometric mean (standard error)				
AUC	31.54 (± 4.35)	51.45 (± 4.02)	46.77 (± 7.74)	

### Statistical analyses

Statistical analysis title	One-way ANOVA
Statistical analysis description: comparison between 3 groups of numerical data	
Comparison groups	hypoxia v normoxia v Hyperoxia



Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.05 <sup>[2]</sup>
Method	ANOVA

Notes:

[1] - Testing for possible difference in TNF outcome

[2] - p=0.0465, there is a difference in AUC of TNF between the 3 groups.

## Secondary: IL-6

End point title	IL-6
End point description:	

End point type	Secondary
End point timeframe:	
1 day	

End point values	hypoxia	normoxia	Hyperoxia	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/ml				
geometric mean (standard error)				
AUC	37.777 (± 6.779)	63.894 (± 10.192)	57.911 (± 11.288)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: IL-8

End point title	IL-8
End point description:	

End point type	Secondary
End point timeframe:	
1 day	

End point values	hypoxia	normoxia	Hyperoxia	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/ml				
geometric mean (standard error)	30.428 (± 3.716)	56.953 (± 5.160)	58.403 (± 6.459)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: IL-10

End point title IL-10

End point description:

End point type Secondary

End point timeframe:

1 day

End point values	hypoxia	normoxia	Hyperoxia	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/ml				
geometric mean (standard error)				
AUC	61.676 ( $\pm$ 10.045)	35.832 ( $\pm$ 4.970)	48.033 ( $\pm$ 11.715)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: PaO2

End point title PaO2

End point description:

End point type Secondary

End point timeframe:

1 day

<b>End point values</b>	hypoxia	normoxia	Hyperoxia	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: kPa				
geometric mean (standard error)				
mean PaO2 between -30min to 150min	5.775 (± 0.195)	15.24 (± 0.729)	54.12 (± 4.14)	

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:  
during experiment

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	hypoxia
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Reporting group description:

subjects were exposed to hypoxia  
for 3.5 h by titration of FiO<sub>2</sub> to a peripheral saturation (SaO<sub>2</sub>) of  
80–85%, using an nitrogen/medical air mixture and an air-tight respiratory  
helmet (CaStar, StarMed, Italy).

Reporting group title	normoxia
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Reporting group description:

medical air, FiO<sub>2</sub> of 21%, also using the respiratory helmet and the same airflow rate as in  
hypoxic subjects,

Reporting group title	Hyperoxia
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Reporting group description:

Subjects will be breathing 100% of oxygen

Serious adverse events	hypoxia	normoxia	Hyperoxia
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	hypoxia	normoxia	Hyperoxia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No adverse events were present during the study

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29983349>