Clinical trial results:
The effects of BCG-vaccination on the innate immune response and immunoparalysis in healthy volunteers

Summary

EudraCT number	2013-005520-42
Trial protocol	NL
Global end of trial date	31 October 2014

Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021
Summary attachment (see zip file)	Gamma-Irradiated Bacille Calmette-Guérin Vaccination Does Not Modulate the Innate Immune Response during Experimental Human Endotoxemia in Adult Males (261864.pdf)

Trial information

Trial identification

Sponsor protocol code	BCG-LPS

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	Jenneke Leentjens, Radboud University Nijmegen Medical Centre, 0031 243668420, jenneke.leentjens@radboudumc.nl
Scientific contact	Jenneke Leentjens, Radboud University Nijmegen Medical Centre, 0031 243668420, jenneke.leentjens@radboudumc.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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2014
Global end of trial reached?	Yes
Global end of trial date	31 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Single endotoxemia
To determine the effects of γ-irradiated BCG-vaccination on the in vivo innate immune responses induced by human endotoxemia. This will be determined by measuring plasma levels of various pro- and anti-inflammatory cytokines and assessing the difference in the Lipopolysacharide (LPS)-induced cytokine response between γ-irradiated BCG-vaccined subjects and placebo-treated control subjects.

2. Repeated endotoxemia
To determine the effects of γ-irradiated BCG-vaccination on endotoxin tolerance induced by human endotoxemia. This will be determined by measuring plasma levels of various pro- and anti-inflammatory cytokines and assessing the difference in the LPS-induced cytokine response following the first and second endotoxemia, between γ-irradiated BCG-vaccined and placebo-treated control subjects.

Protection of trial subjects:

Volunteers gave written informed consent to participate in this study. Throughout the study period, subjects were not allowed to take any drugs, including cetaminophen, and were asked to refrain from alcohol and caffeine 24 hours and from food 12 hours before the start of the endotoxemia experiment. All study procedures were conducted in accordance with the declaration of Helsinki including current revisions and Good Clinical Practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

20 healthy nonsmoking male volunteers gave written informed consent to participate in this study.

Pre-assignment

Screening details:

Subjects were screened before the start of the experiment and had a normal physical examination, electrocardiography,
and routine laboratory values.

Period 1

Period 1 title	In study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	BCG vaccination

Arm description: -

Arm type	Experimental
Investigational medicinal product name	γ-Irradiated BCG vaccine
Investigational medicinal product code	
Other name	γ-Irradiated BCG vaccine (BCG-Vaccin SSI [Nederlands Vaccin Instituut]) Danish strain 1331
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 0.075 mg (0.1mL) gamma-irradiated BCG vaccine intracutaneously (BCG vaccine SSI; Statens Serum Institut, gamma-irradiation (25–30 kGy) performed by Synergy Health Ede, Netherlands

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	BCG-reconstitution fluid: diluted Sauton 1+3; Statens Serum Institut
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received 0.1mL placebo intracutaneously

Number of subjects in period 1	BCG vaccination	Placebo
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups	
Reporting group title	BCG vaccination
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	BCG vaccination	Placebo	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	20
Age continuous Units: years			
median	20.5	20	
inter-quartile range (Q1-Q3)	19.8 to 22	19 to 24.3	-
Gender categorical Units: Subjects			
Male	10	10	20

End points

End points reporting groups	
Reporting group title	BCG vaccination
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: TNF-alpha	
End point title	TNF-alpha
End point description:	
End point type	Primary
End point timeframe:	
Area under the curve after LPS injection (until day 10 after injection)	

End point values	BCG vaccination	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: pg/mL.hour				
median (inter-quartile range (Q1-Q3))	650 (400 to 800)	700 (490 to 1200)		

Statistical analyses

Statistical analysis title	TNF-alpha, BCG vs. placebo
Comparison groups	BCG vaccination v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: IL-6	
End point title	IL-6
End point description:	
End point type	Primary
End point timeframe:	
Area under the curve after LPS injection (until day 10 after injection)	

End point values	BCG vaccination	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: pg/mL.hour				
median (inter-quartile range (Q1-Q3))	450 (300 to 650)	670 (380 to 850)		

Statistical analyses

Statistical analysis title	IL-6, BCG vs. placebo
Comparison groups	BCG vaccination v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After vaccination	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	BCG vaccination
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	BCG vaccination	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BCG vaccination	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	1 / 10 (10.00%)	
Skin and subcutaneous tissue disorders			
Scar			
subjects affected / exposed	9 / 10 (90.00%)	1 / 10 (10.00%)	
occurrences (all)	9	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1) Inactivation of the vaccine
2) Timing of interventions
3) Only male
4) Training effects of BCG nullified by LPS
5) Human endotoxemia model is mild
6) No pre-screening of subjects for previous exposure to Mycobacterium tuberculosis

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25883989