Clinical trial results:
The effects of endotoxin challenge on the immune response elicited by a subsequent challenge with Fluenz™ in healthy volunteers, a pilot study

Summary

EudraCT number	2015-004023-31
Trial protocol	NL
Global end of trial date	26 February 2016

Results information

Result version number	v1 (current)
This version publication date	08 July 2022
First version publication date	08 July 2022
Summary attachment (see zip file)	Development of Endotoxin Tolerance Does Not Influence the Response to a Challenge with the Mucosal Live-Attenuated Influenza Vaccine in Humans In Vivo (Development of Endotoxin Tolerance Does Not Influence the Response to a Challenge with the Mucosal Live-Attenuated Influenza Vaccine in Humans In Vivo.pdf)

Trial information

Trial identification

Sponsor protocol code	LPS-Fluenz

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02642237
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	Research IC, office of Rebecca Koch, Radboudumc, rebecca.koch@radboudumc.nl
Scientific contact	Research IC, office of Rebecca Koch, Radboudumc, rebecca.koch@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	26 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2016
Global end of trial reached?	Yes
Global end of trial date	26 February 2016
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 investigate the effects of an endotoxin challenge and subsequent development of endotoxin tolerance on the local immune response following Fluenz™ administration in vivo. The primary outcome measure is the difference in concentrations of CXCL-10 in nasal wash between subjects in the placebo-Fluenz™ group and the LPS-Fluenz™ group.

Protection of trial subjects:

All subjects provided written informed consent, all subjects were healthy. Subjects were asked to refrain from caffeine and alcohol intake 24 h, and from food 12 h before the LPS/placebo challenge.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

30 healthy, non-smoking male subjects aged 18–35 years gave written informed consent to participate in the study

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	30
Number of subjects completed	30

Period 1

Period 1 title	LPS/placebo challenge
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Intravenous bolus injection 0.9% saline

Arm title	Lipopolysaccharide (LPS)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Lipopolysaccharide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Intravenous bolus administration of LPS (2 ng/kg)

Number of subjects in period 1	Placebo	Lipopolysaccharide (LPS)
Started	15	15
Completed	15	15

Period 2	
Period 2 title	Viral challenge
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo+Fluenz
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intravenous bolus use
Dosage and administration details: Intravenous bolus injection 0.9% saline	
Investigational medicinal product name	Live-attenuated quadrivalent influenza vaccine (LAIV) Fluenz Tetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use
Dosage and administration details: Intranasal vaccination with the live-attenuated quadrivalent influenza vaccine (LAIV) Fluenz Tetra (0.1 ml/nostril). Subjects remained in the recumbent position for 1 min after Fluenz administration.	
Arm title	LPS+Fluenz
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lipopolysaccharide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use
Dosage and administration details: Intravenous bolus administration of LPS (2 ng/kg)	
Investigational medicinal product name	Live-attenuated quadrivalent influenza vaccine (LAIV) Fluenz Tetra
Investigational medicinal product code	

Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Intranasal vaccination with the live-attenuated quadrivalent influenza vaccine (LAIV) Fluenz Tetra (0.1 ml/nostril). Subjects remained in the recumbent position for 1 min after Fluenz administration.

Number of subjects in period 2	Placebo+Fluenz	LPS+Fluenz
Started	15	15
Completed	13	13
Not completed	2	2
No viral load	1	2
Co-infection	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Lipopolysaccharide (LPS)
Reporting group description: -	

Reporting group values	Placebo	Lipopolysaccharide (LPS)	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	30
Age continuous Units: years			
median	21	22	
inter-quartile range (Q1-Q3)	20 to 23	19 to 23	-
Gender categorical Units: Subjects			
Male	15	15	30

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Lipopolysaccharide (LPS)
Reporting group description: -	
Reporting group title	Placebo+Fluenz
Reporting group description: -	
Reporting group title	LPS+Fluenz
Reporting group description: -	

Primary: Viral load, Influenza A

End point title	Viral load, Influenza A
End point description:	
End point type	Primary
End point timeframe:	
Subjects were challenged with LPS/Placebo on day 0, tested if viral load was present at day 7. Measurements of viral load on day 8	

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Fold change				
geometric mean (confidence interval 95%)				
Day 8	16 (10 to 27)	26 (20 to 83)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Placebo+Fluenz v LPS+Fluenz
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.54
Method	Wilcoxon (Mann-Whitney)

Primary: Viral load, Influenza B

End point title	Viral load, Influenza B

End point description:

End point type	Primary

End point timeframe:

Subjects were challenged with LPS/Placebo on day 0, tested if viral load was present at day 7. Measurements of viral load on day 8

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Fold change				
geometric mean (confidence interval 95%)				
Day 8	29 (20 to 64)	14 (11 to 40)		

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	Placebo+Fluenz v LPS+Fluenz
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.45
Method	Wilcoxon (Mann-Whitney)

Secondary: IgG seroconversion, A/H1N1

End point title	IgG seroconversion, A/H1N1

End point description:

End point type	Secondary

End point timeframe:

Subjects were challenged with LPS/Placebo on day 0 and displayed infectivity after inoculation with Fluenz on day 7. Seroconverted subjects were counted on day 35.

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Seroconverted individuals	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: IgG seroconversion, A/H3N2

End point title	IgG seroconversion, A/H3N2

End point description:

End point type	Secondary

End point timeframe:

Subjects were challenged with LPS/Placebo on day 0 and displayed infectivity after inoculation with Fluenz on day 7. Seroconverted subjects were counted on day 35.

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Seroconverted subjects	11	10		

Statistical analyses

No statistical analyses for this end point

Secondary: IgG seroconversion, B/Phuket

End point title	IgG seroconversion, B/Phuket

End point description:

End point type	Secondary

End point timeframe:

Subjects were challenged with LPS/Placebo on day 0 and displayed infectivity after inoculation with Fluenz on day 7. Seroconverted subjects were counted on day 35.

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Seroconverted subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: IgG seroconversion, B/Brisbane

End point title	IgG seroconversion, B/Brisbane

End point description:

End point type	Secondary

End point timeframe:

Subjects were challenged with LPS/Placebo on day 0 and displayed infectivity after inoculation with Fluenz on day 7. Seroconverted subjects were counted on day 35.

End point values	Placebo+Fluenz	LPS+Fluenz		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Seroconverted subjects	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Throughout complete study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE guidelines
Dictionary version	4.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Lipopolysaccharide (LPS)
Reporting group description: -	

Serious adverse events	Placebo	Lipopolysaccharide (LPS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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	Placebo	Lipopolysaccharide (LPS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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 non-serious adverse events were recorded.

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.

Study was performed during winter season (possible viral co-infections)

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29312282