Clinical trial results:
Investigation of the anti-inflammatory effects of simvastatin in a model of acute lung injury after inhalation of lipopolysaccharide by healthy volunteers

Summary

EudraCT number	2006-004396-35
Trial protocol	GB
Global end of trial date	10 November 2013

Results information

Result version number	v1 (current)
This version publication date	23 December 2019
First version publication date	23 December 2019

Trial information

Trial identification

Sponsor protocol code	06078SE-A

Additional study identifiers

ISRCTN number	ISRCTN21056528
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health & Social Care Trust (BHSCT)
Sponsor organisation address	King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, d.f.mcauley@qub.ac.uk
Scientific contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, d.f.mcauley@qub.ac.uk

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	22 October 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2008
Global end of trial reached?	Yes
Global end of trial date	10 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The hypothesis of the study is that treatment with simvastatin for 4 days will reduce pulmonary inflammation induced by LPS inhalation in humans.

The primary outcome measure will be a reduction in bronchoalveolar lavage (BAL) CXCL8 concentration between the simvastatin and placebo treated groups.

Protection of trial subjects:

A DMEC was appointed which was independent of the study team and comprised of two clinicians with experience in undertaking clinical trials, and a statistician. The DMEC met to agree conduct and remit which included an early termination process. The DMEC met after the first 2 participants have been enrolled into the study and met after every 10 participants thereafter. An interim analysis of efficacy was not planned. The DMEC functioned primarily as a check for safety, reviewing adverse events. The DMEC reported to the Sponsor via the principal investigator.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 January 2007
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	United Kingdom: 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	0

months)	
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:

Healthy subjects were recruited by advertising.

Pre-assignment

Screening details:

Screening consisting of a questionnaire, physical examination, routine blood investigation, ECG, and measurement of lung function with spirometry (FEV1 and FVC) was performed.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Blinding of the simvastatin tablets and placebo was achieved by encapsulation with a gelatin capsule. The simvastatin capsule contained the simvastatin tablet with lactose powder. The placebo capsule contained lactose powder only. Both the simvastatin and placebo study drugs had an identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	Simvastatin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Simvastatin 40 mg and 80mg for 4 days

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 days

Number of subjects in period 1	Simvastatin	Placebo
Started	20	10
Completed	20	10

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Simvastatin	Placebo	Total
Number of subjects	20	10	30
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)	20	10	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	25.8	25.8	
standard deviation	± 6.01	± 4.49	-
Gender categorical Units: Subjects			
Female	11	5	16
Male	9	5	14
height Units: metres			
arithmetic mean	1.69	1.68	
standard deviation	± 0.08	± 0.08	-
weight Units: kg			
arithmetic mean	68.13	74.17	
standard deviation	± 10.58	± 9.58	-
FEV1 Units: litres			
arithmetic mean	3.60	3.88	
standard deviation	± 0.67	± 0.73	-
FVC Units: litres			
arithmetic mean	4.27	4.58	
standard deviation	± 0.81	± 0.92	-

End points

End points reporting groups	
Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: IL-8	
End point title	IL-8
End point description:	
End point type	Primary
End point timeframe:	
6 hours after inhalation of LPS	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: units				
median (inter-quartile range (Q1-Q3))	315.3 (190.1 to 497.4)	381.8 (317.1 to 463.7)		

Statistical analyses

Statistical analysis title	comparison of 2 groups
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Wilcoxon (Mann-Whitney)

Secondary: total cells	
End point title	total cells
End point description:	
End point type	Secondary
End point timeframe:	
6 hours after inhalation of LPS	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: 10*5/ml				
median (inter-quartile range (Q1-Q3))	10.7 (4.6 to 17.4)	15.2 (10.3 to 49.8)		

Statistical analyses

Statistical analysis title	total cells comparison of 2 groups
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Secondary: neutrophils

End point title	neutrophils

End point description:

End point type	Secondary

End point timeframe:

6 hours after inhalation of LPS

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: units				
median (inter-quartile range (Q1-Q3))	3.0 (1.8 to 8.1)	8.5 (4.4 to 16.2)		

Statistical analyses

Statistical analysis title	neutrophils comparison of 2 groups
Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: macrophages

End point title	macrophages

End point description:

End point type	Secondary

End point timeframe:

6 hours after inhalation of LPS

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: units				
median (inter-quartile range (Q1-Q3))	5.1 (2.1 to 13.0)	7.0 (3.1 to 19.1)		

Statistical analyses

Statistical analysis title	macrophages comparison of 2 groups
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Wilcoxon (Mann-Whitney)

Secondary: lymphocytes

End point title	lymphocytes

End point description:

End point type	Secondary

End point timeframe:

6 hours after inhalation of LPS

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: units				
median (inter-quartile range (Q1-Q3))	0.9 (0.2 to 1.6)	1.1 (0.6 to 3.2)		

Statistical analyses

Statistical analysis title	lymphocytes comparison of 2 groups
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 24 hrs after LPS inhalational	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (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: 0 %

Non-serious adverse events	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	5 / 10 (50.00%)	
Investigations			
Asymptomatic elevated CK			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Fall in FEV1			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Nervous system disorders			
Migraine 3 days after starting study medication and took NSAIDS. Did not have LPS inhalation or BAL			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Chest pain and fall in FEV1 (unable to take deep breath)			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
URTI 2 days after starting study medication. Family had similar symptoms. Did not have LPS inhalatio			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
URTI 3 days after starting study medication. Did not have LPS inhalation or BAL			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2007	To increase the duration of the study by 2 years
22 April 2009	To request an extension for sample analysis only
30 December 2009	Amendment to protocol: measurement of plasma and BAL serine protease and anti-protease activity and mRNA analysis for additional proteases and other proteins modulating the inflammatory response

Notes:

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.

None reported.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19324974