Clinical trial results:
Investigation of the protective effects of keratinocyte growth factor (KGF) in a human lipopolysaccharide induced model of acute lung injury

Summary

EudraCT number	2008-000441-58
Trial protocol	GB
Global end of trial date	09 April 2015

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020
Summary attachment (see zip file)	Figures from publication (Figures KGF MArch 2014 R2.pptx) Figures from supplementary section of publication (KGF suppl data figures Fb2014.pptx) Am J Respir Crit Care Med publication (KGF in LPS model.pdf)

Trial information

Trial identification

Sponsor protocol code	08005DM-A

Additional study identifiers

ISRCTN number	ISRCTN98813895
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	17 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2013
Global end of trial reached?	Yes
Global end of trial date	09 April 2015
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 a clinically relevant dose of KGF reduces pulmonary and systemic inflammation induced by LPS inhalation in humans.

The primary endpoint of this study is to evaluate the ability of KGF to reduce alveolar epithelial injury, as measured by BAL RAGE concentration, between the KGF and placebo treated groups.

All outcomes are BAL.

Protection of trial subjects:

A DMEC was appointed which was independent of the study team. The DMEC met to agree conduct and remit which included an early termination process. 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	08 August 2008
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	39
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:

When an eligible subject was recruited, the clinical trials pharmacist was contacted with the subject details. The medication was prepared by the pharmacist according to guidance in a covered syringe thereby maintaining blinding. Both the active and placebo treatment had an identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Keratinocyte growth factor (KGF)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Keratinocyte growth factor
Investigational medicinal product code	
Other name	palifermin
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

60 µg/kg per day for 3 days

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

3 days

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

3 days

Number of subjects in period 1	Keratinocyte growth factor (KGF)	Placebo
Started	19	20
Completed	16	20
Not completed	3	0
Adverse event, non-fatal	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Keratinocyte growth factor (KGF)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Keratinocyte growth factor (KGF)	Placebo	Total
Number of subjects	19	20	39
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)	19	20	39
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	23.6	26.1	
standard deviation	± 5.2	± 5.9	-
Gender categorical Units: Subjects			
Female	10	11	21
Male	9	9	18
height Units: cm			
arithmetic mean	171	170	
standard deviation	± 10.4	± 9.0	-
weight Units: kg			
arithmetic mean	68	71	
standard deviation	± 9	± 11	-
FEV1 Units: litres			
arithmetic mean	3.8	3.8	
standard deviation	± 0.8	± 0.7	-

End points

End points reporting groups	
Reporting group title	Keratinocyte growth factor (KGF)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: RAGE	
End point title	RAGE
End point description:	
End point type	Primary
End point timeframe:	
24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ng/ml				
arithmetic mean (standard deviation)	4.2 (± 1.0)	3.5 (± 1.5)		

Statistical analyses

Statistical analysis title	RAGE comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	t-test, 2-sided

Secondary: WBC count	
End point title	WBC count
End point description:	
white blood count	
End point type	Secondary
End point timeframe:	
24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: 10*5/ml				
median (inter-quartile range (Q1-Q3))	5.5 (3.6 to 8.4)	5.3 (4.0 to 7.6)		

Statistical analyses

Statistical analysis title	WBC count comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: albumin

End point title	albumin

End point description:

End point type	Secondary

End point timeframe:

24 hours after LPS inhalation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: mg/l				
median (inter-quartile range (Q1-Q3))	64.6 (49.2 to 111.6)	58.7 (44.4 to 84.5)		

Statistical analyses

Statistical analysis title	albumin comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: IL-1Ra

End point title	IL-1Ra

End point description:

End point type	Secondary

End point timeframe:

24 hours after LPS inhalation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	5.02 (3.78 to 9.50)	3.41 (1.73 to 5.42)		

Statistical analyses

Statistical analysis title	IL-1Ra comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Secondary: IL-1b/IL-1Ra ratio

End point title	IL-1b/IL-1Ra ratio

End point description:

End point type	Secondary

End point timeframe:

24 hours after LPS inhalation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ratio				
median (inter-quartile range (Q1-Q3))	0.004 (0.003 to 0.007)	0.009 (0.005 to 0.014)		

Statistical analyses

Statistical analysis title	IL-1b/IL-1Ra ratio comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Secondary: IL-1b

End point title	IL-1b

End point description:

End point type	Secondary

End point timeframe:

24 hours after LPS inhalation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	25.7 (15.1 to 48.6)	29.0 (13.9 to 41.7)		

Statistical analyses

Statistical analysis title	IL-1b comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: TNF-a	
End point title	TNF-a
End point description: tumor necrosis factor	
End point type	Secondary
End point timeframe: 24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	63.5 (40.0 to 96.0)	46.0 (20.9 to 65.6)		

Statistical analyses

Statistical analysis title	TNF-a comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: IL-6	
End point title	IL-6
End point description:	
End point type	Secondary
End point timeframe: 24 hours after inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	527 (228 to 1154)	350 (175 to 512)		

Statistical analyses

Statistical analysis title	IL-6 comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: IL-8

End point title	IL-8

End point description:

End point type	Secondary

End point timeframe:

24 hours after LPS inhalation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	336 (290 to 436)	289 (197 to 457)		

Statistical analyses

Statistical analysis title	IL-8 comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: VEGF	
End point title	VEGF
End point description: vascular endothelial growth factor	
End point type	Secondary
End point timeframe: 24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	140 (110 to 193)	122 (93.5 to 213)		

Statistical analyses

Statistical analysis title	VEGF comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: MCP-1	
End point title	MCP-1
End point description: monocyte chemoattractant protein	
End point type	Secondary
End point timeframe: 24 hours after inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	520 (366 to 684)	347 (210 to 532)		

Statistical analyses

Statistical analysis title	MCP-1 comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: HMGB1

End point title	HMGB1
End point description: high-mobility group box 1	
End point type	Secondary
End point timeframe: 24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	21.8 (13.2 to 30.7)	16.7 (9.9 to 34.8)		

Statistical analyses

Statistical analysis title	HMGB1 comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Calgranulin C	
End point title	Calgranulin C
End point description:	
End point type	Secondary
End point timeframe:	
24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	34.7 (18.5 to 49.5)	28.6 (13.3 to 56.4)		

Statistical analyses

Statistical analysis title	Calgranulin C comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: CRP	
End point title	CRP
End point description:	
C-reactive protein	
End point type	Secondary
End point timeframe:	
24 hours after LPS inhalation	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	491 (296 to 968)	161 (62 to 392)		

Statistical analyses

Statistical analysis title	CRP comparison of groups
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
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: 24 hours after LPS inhalation	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	Keratinocyte growth factor (KGF)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Keratinocyte growth factor (KGF)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 20 (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	Keratinocyte growth factor (KGF)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	6 / 20 (30.00%)	
Investigations			
Liver function			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Altered taste			
subjects affected / exposed	5 / 19 (26.32%)	3 / 20 (15.00%)	
occurrences (all)	5	3	
Tingling in toes			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders			
Oral tingling			
subjects affected / exposed	5 / 19 (26.32%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Tongue swelling			
subjects affected / exposed	2 / 19 (10.53%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Tongue disorder			
subjects affected / exposed	2 / 19 (10.53%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Tongue Discolouration			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lip disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	8 / 19 (42.11%)	1 / 20 (5.00%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 December 2008	To source the study medication from Biovitrum
22 January 2009	To increase the number of volunteers undergoing bronchoscopy and BAL from 5 to 10; to recruit 5 volunteers who undergo bronchoscopy and BAL after pre treatment with 3 days for KGF at a dose of 60 microgram/kg; to isolate alveolar macrophages from BAL and study them in vitro
30 December 2009	To measure the serine protease and anti protease activity in plasma samples

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.
An additional 15 control subjects were enrolled. In keeping with the study protocol these subjects were not randomised to receive IMP.
In addition to the Endpoints section, other outcomes are presented graphically in the attachments.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24716610