Clinical trial results:

Keratinocyte growth factor in Acute lung injury to REduce pulmonary dysfunction – a randomised placebo controlled trial (KARE)

Summary

EudraCT number	2010-021186-70
Trial protocol	GB
Global end of trial date	17 August 2017

Results information

Result version number	v1 (current)
This version publication date	24 May 2019
First version publication date	24 May 2019

Trial information

Trial identification

Sponsor protocol code	10089DMCA-CS

Additional study identifiers

ISRCTN number	ISRCTN95690673
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 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2017
Global end of trial reached?	Yes
Global end of trial date	17 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to test the hypothesis that palifermin will be effective in the treatment of patients with acute lung injury (ALI).

The trial objective is to undertaken a randomised double blind placebo controlled (i.e. dummy medication) clinical trial to study whether palifermin improves important surrogate markers of clinical outcome and is safe in adult patients with ALI in intensive care.

Protection of trial subjects:

Patients were closely monitored for AEs.
A Clinical Trials Monitor monitored study site compliance with study and sponsor SOPs and provided feedback to the Trial Management Group on any actual or potential problems in relation to safeguarding patients safety and wellbeing.
The DMEC was appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients. The DMEC met regularly and meetings were formally minuted. The DMEC's responsibility was to safeguard patient safety. The DMEC monitored recruitment and adverse event data. All AEs/SAEs were assessed for expectedness, causality and severity. All AEs were assessed as possibly, probably or definitely related to the study drug.
We originally intended that any events that are normally expected in this population would not be recorded as serious adverse events; however, the approved protocol stated that all serious adverse events that occurred would be reported, regardless of the underlying association to the underlying clinical condition. Subsequently all serious adverse events were reported and the association to underlying clinical condition was recorded.
All of the serious adverse events were assessed by the chief investigator and an independent intensive care unit physician as being due to the patient's underlying medical condition and unrelated to the study drug.

Background therapy:	
Not applicable	
Evidence for comparator:	
Not applicable	
Actual start date of recruitment	23 February 2011
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: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	35
From 65 to 84 years	23
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Between Feb 23, 2011, and Feb 26, 2014, 368 patients were assessed for eligibility and 60 patients recruited in UK.

Pre-assignment

Screening details:

Patients ≥ 16 years, intubated and mechanically ventilated with partial pressure of arterial oxygen to fractional inspired oxygen concentration ratio of 300 mmHg or less, with bilateral pulmonary infiltrates consistent with pulmonary oedema present on chest x-ray, and no evidence of left atrial hypertension. 368 screened, 60 randomised.

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:

Patients and investigators were both masked to treatment. The study drug was stored in a masked container in a locked fridge. A trained member of the intensive care unit nursing staff who was not involved in the clinical trial removed the study drug container from the fridge and brought it to the bedside,
where the study drug was reconstituted and administered intravenously to the unconscious patient, before returning the masked study drug container to the fridge.

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 infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

60 μg/kg per day for 6 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:

0·9% sodium chloride solution for 6 days

Number of subjects in period 1	Keratinocyte growth factor (KGF)	Placebo
Started	29	31
Completed	29	31

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	29	31	60
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)	18	17	35
From 65-84 years	11	12	23
85 years and over	0	2	2
Age continuous			
Units: years			
arithmetic mean	55.6	61	
standard deviation	± 17.5	± 15.4	-
Gender categorical			
Units: Subjects			
Female	12	11	23
Male	17	20	37
Sepsis requiring vasopressors			
Units: Subjects			
sepsis	14	15	29
non-sepsis	15	16	31
Cause of ARDS - Smoke or toxin inhalation			
Units: Subjects			
yes	1	0	1
no	28	31	59
Cause of ARDS - Aspiration			
Units: Subjects			
yes	10	7	17
no	19	24	43
Cause of ARDS - Thoracic trauma			
Units: Subjects			
yes	1	2	3
no	28	29	57
Cause of ARDS - Pneumonia			

Units: Subjects			
yes	10	18	28
no	19	13	32
Cause of ARDS - Sepsis			
Units: Subjects			
yes	11	16	27
no	18	15	33
Cause of ARDS - Pancreatitis			
Units: Subjects			
yes	0	2	2
no	29	29	58
Cause of ARDS - Non-thoracic trauma			
Units: Subjects			
yes	5	1	6
no	24	30	54
Cause of ARDS - Other			
Units: Subjects			
yes	3	2	5
no	26	29	55
APACHE II			
Units: score			
arithmetic mean	18.8	22.7	
standard deviation	± 9.0	± 6.5	-
LIS			
Units: score			
arithmetic mean	2	2.2	
standard deviation	± 0.6	± 0.6	-
Mean arterial pressure			
Units: mmHg			
arithmetic mean	63.5	64.5	
standard deviation	± 11.2	± 10.3	-
Tidal Volume at randomisation			
Units: ml/kg PBW			
arithmetic mean	7.9	8.3	
standard deviation	± 2.6	± 2.1	-
PEEP			
Units: cm H2O			
arithmetic mean	7.3	8.5	
standard deviation	± 2.2	± 2.4	-
Plateau pressure			
Units: cm H2O			
arithmetic mean	23.3	24	
standard deviation	± 4.7	± 3.3	-
Oxygenation index			
Units: kPa			
arithmetic mean	72.3	103.2	
standard deviation	± 51.6	± 60.2	-
PaO2/FiO2 ratio			
Units: kPa			
arithmetic mean	21.4	15.8	
standard deviation	± 8.6	± 5.7	-

Compliance Units: ml/cm H2O			
arithmetic mean	40.1	43.9	
standard deviation	± 16.3	± 15.8	-
SOFA Units: score			
arithmetic mean	9.5	8.9	
standard deviation	± 4.0	± 3.1	-
airway pressure Units: cm H20			
arithmetic mean	12.2	13.9	
standard deviation	± 4.2	± 4.1	-

End points

End points reporting groups

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

Primary: Oxygenation index (last available) day 7

End point title	Oxygenation index (last available) day 7
End point description:	
End point type	Primary
End point timeframe: day 7	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: kPa				
arithmetic mean (standard deviation)	62.3 (± 57.8)	43.1 (± 33.5)		

Statistical analyses

Statistical analysis title	OI day 7
Comparison groups	Placebo v Keratinocyte growth factor (KGF)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	19.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	44

Secondary: Oxygenation index (last available) day 3

End point title	Oxygenation index (last available) day 3
End point description:	
End point type	Secondary
End point timeframe:	
day 3	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: kPa				
arithmetic mean (standard deviation)	66.9 (± 55.0)	60.1 (± 45.4)		

Statistical analyses

Statistical analysis title	OI day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.2
upper limit	32.8

Secondary: Oxygenation index (last available) day 14

End point title	Oxygenation index (last available) day 14
End point description:	
End point type	Secondary
End point timeframe:	
day 14	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: kPa				
arithmetic mean (standard deviation)	59.4 (± 58.4)	30.1 (± 24.2)		

Statistical analyses

Statistical analysis title	OI day 14
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	53

Secondary: Oxygenation index (measured) day 3

End point title	Oxygenation index (measured) day 3
End point description:	
End point type	Secondary
End point timeframe:	
day 3	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: kPa				
arithmetic mean (standard deviation)	62.8 (± 50.1)	60.9 (± 45.9)		

Statistical analyses

Statistical analysis title	OI day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.9
upper limit	27.6

Secondary: Oxygenation index (measured) day 7

End point title	Oxygenation index (measured) day 7
End point description:	

End point type	Secondary
End point timeframe:	
day 7	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: kPa				
arithmetic mean (standard deviation)	45.4 (± 32.1)	48.6 (± 38.6)		

Statistical analyses

Statistical analysis title	OI day 7
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.8
upper limit	18.3

Secondary: Oxygenation index (measured) day 14

End point title	Oxygenation index (measured) day 14
End point description:	
End point type	Secondary
End point timeframe:	
day 14	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: kPa				
arithmetic mean (standard deviation)	52.9 (± 35.2)	43.3 (± 37.2)		

Statistical analyses

Statistical analysis title	OI day 14
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.8
upper limit	51

Secondary: Respiratory compliance day 3

End point title	Respiratory compliance day 3

End point description:	
End point type	Secondary
End point timeframe:	
day 3	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: mL/cm H2O				
arithmetic mean (standard deviation)	48.6 (± 16.4)	53.5 (± 28.8)		

Statistical analyses

Statistical analysis title	Respiratory compliance day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	11.6

Secondary: Respiratory compliance day 7	
End point title	Respiratory compliance day 7
End point description:	
End point type	Secondary
End point timeframe:	
day 7	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: mL/cm H2O				
arithmetic mean (standard deviation)	51.1 (± 25.2)	65.1 (± 15.4)		

Statistical analyses

Statistical analysis title	Respiratory compliance day 7
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.9
upper limit	7.9

Secondary: Respiratory compliance day 14

End point title	Respiratory compliance day 14
End point description:	
End point type	Secondary
End point timeframe:	
day 14	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	1		
Units: mL/cm H2O				
arithmetic mean (standard deviation)	45.0 (± 10.4)	77.5 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PaO2/FiO2 ratio day 3

End point title	PaO2/FiO2 ratio day 3
End point description:	
End point type	Secondary
End point timeframe:	
day 3	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	31		
Units: kPa				
arithmetic mean (standard deviation)	23.1 (± 9.1)	20.3 (± 6.0)		

Statistical analyses

Statistical analysis title	PaO2/FiO2 ratio day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	7.1

Secondary: PaO2/FiO2 ratio day 7

End point title	PaO2/FiO2 ratio day 7
End point description:	
End point type	Secondary
End point timeframe:	
day 7	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: kPa				
arithmetic mean (standard deviation)	27.6 (± 10.4)	24.6 (± 7.6)		

Statistical analyses

Statistical analysis title	PaO2/FiO2 ratio day 7
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	8.6

Secondary: PaO2/FiO2 ratio day 14

End point title	PaO2/FiO2 ratio day 14
End point description:	
End point type	Secondary
End point timeframe: day 14	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: kPa				
arithmetic mean (standard deviation)	27.2 (± 12.0)	21.3 (± 9.0)		

Statistical analyses

Statistical analysis title	PaO2/FiO2 ratio day 14
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	17.2

Secondary: SOFA day 3

End point title	SOFA day 3
End point description:	

End point type	Secondary
End point timeframe:	
day 3	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	29		
Units: score				
arithmetic mean (standard deviation)	7.6 (± 3.6)	7.8 (± 4.0)		

Statistical analyses

Statistical analysis title	SOFA day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	2

Secondary: SOFA day 7

End point title	SOFA day 7
End point description:	
End point type	Secondary
End point timeframe:	
day 7	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	6.7 (± 3.0)	7.9 (± 4.1)		

Statistical analyses

Statistical analysis title	SOFA day 7
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.5

Secondary: SOFA day 14

End point title	SOFA day 14

End point description:

End point type	Secondary

End point timeframe:

day 14

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: score				
arithmetic mean (standard deviation)	6.9 (± 2.0)	5.9 (± 2.8)		

Statistical analyses

Statistical analysis title	SOFA day 14
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.5

Secondary: Change in SOFA from baseline to day 3

End point title	Change in SOFA from baseline to day 3

End point description:

End point type	Secondary

End point timeframe:

day 3

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: score				
arithmetic mean (standard deviation)	-1.4 (± 1.9)	-1.2 (± 2.3)		

Statistical analyses

Statistical analysis title	Change in SOFA from baseline to day 3
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1

Secondary: Change in SOFA from baseline to day 7

End point title	Change in SOFA from baseline to day 7

End point description:

End point type	Secondary

End point timeframe:

day 7

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: score				
arithmetic mean (standard deviation)	-2.9 (± 2.7)	-2.0 (± 3.0)		

Statistical analyses

Statistical analysis title	Change in SOFA from baseline to day 7
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1.3

Secondary: Change in SOFA from baseline to day 14

End point title	Change in SOFA from baseline to day 14
End point description:	
End point type	Secondary
End point timeframe:	
day 14	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: score				
arithmetic mean (standard deviation)	-2.3 (± 1.7)	-3.9 (± 3.8)		

Statistical analyses

Statistical analysis title	Change in SOFA from baseline to day 14
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	4.6

Secondary: Ventilator-free days to day 28

End point title	Ventilator-free days to day 28
End point description:	
End point type	Secondary
End point timeframe:	
up to 28 days	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: days				
median (inter-quartile range (Q1-Q3))	1 (0 to 17)	20 (13 to 22)		

Statistical analyses

Statistical analysis title	Ventilator-free days to day 28
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	-2

Secondary: Duration of ventilation

End point title	Duration of ventilation

End point description:

End point type	Secondary

End point timeframe:

Duration of ventilation

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: days				
median (inter-quartile range (Q1-Q3))	16 (13 to 30)	11 (8 to 16)		

Statistical analyses

Statistical analysis title	Duration of ventilation
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	14

Secondary: ICU stay

End point title	ICU stay

End point description:

End point type	Secondary

End point timeframe:
ICU stay

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: days				
median (inter-quartile range (Q1-Q3))	22 (14 to 32)	12 (10 to 19)		

Statistical analyses

Statistical analysis title	ICU stay
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	17

Secondary: Hospital length of stay

End point title	Hospital length of stay

End point description:

End point type	Secondary

End point timeframe:
Hospital stay

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: days				
median (inter-quartile range (Q1-Q3))	39 (30 to 67)	23 (18 to 33)		

Statistical analyses

Statistical analysis title	Hospital length of stay
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	17
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	33

Secondary: 28-day mortality

End point title	28-day mortality
End point description:	

End point type	Secondary
End point timeframe:	
28 days	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: subjects	9	3		

Statistical analyses

Statistical analysis title	28-day mortality
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	10.7

Secondary: 90-day mortality

End point title	90-day mortality
End point description:	

End point type	Secondary
End point timeframe:	
90 days	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: subjects	13	5		

Statistical analyses

Statistical analysis title	90-day mortality
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	6.8

Secondary: ICU mortality

End point title	ICU mortality

End point description:

End point type	Secondary

End point timeframe:
ICU stay

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: subjects	12	2		

Statistical analyses

Statistical analysis title	ICU mortality
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	26.2

Secondary: Hospital mortality

End point title	Hospital mortality

End point description:

End point type	Secondary
End point timeframe:	
Hospital stay	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: subjects	14	4		

Statistical analyses

Statistical analysis title	Hospital mortality
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	10.1

Secondary: 1-year mortality

End point title	1-year mortality
End point description:	
End point type	Secondary
End point timeframe:	
1 year	

End point values	Keratinocyte growth factor (KGF)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: subjects	15	8		

Statistical analyses

Statistical analysis title	1-year mortality
Comparison groups	Keratinocyte growth factor (KGF) v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events that occur between trial entry and up to 28 days after completion of the study drug will be reported.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Keratinocyte growth factor (KGF)

Reporting group description:

Patients on KGF who experienced an adverse event

Reporting group title	Placebo

Reporting group description:

Patients on placebo who experienced an adverse event

Serious adverse events	Keratinocyte growth factor (KGF)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 29 (41.38%)	4 / 31 (12.90%)	
number of deaths (all causes)	11	4	
number of deaths resulting from adverse events	11	4	
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction and ruptured aortic aneurysm and metastatic pancreatic cancer			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Severe hypoxic brain injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haematoma and midline			

shift and intraventricular subdural haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

General disorders and administration site conditions

Variceal bleed multi-organ failure chronic liver failure hepatitis C			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ruptured aortic aneurysm with subsequent multi-organ failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multi-organ failure gram negative sepsis chronic liver disease			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-organ failure, pulmonary haemorrhage, PCJ pneumonia and alcohol related liver disease.			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multi-organ failure due to sepsis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis and ongoing pancreatitis and multi-organ failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multi organ failure and sepsis			

	Keratinocyte growth factor (KGF)	Placebo	
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Pancreatitis contributing to prolonged hospitalisation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Alcohol liver disease			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
COPD and type 2 respiratory failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Obstructive hydrocephalus gram negative sepsis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic fungal infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	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	2 / 29 (6.90%)	1 / 31 (3.23%)	

General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Maculopapular Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	Changes to inclusion/exclusion criteria – extend to 72 hours post onset of acute lung injury; inclusion of patients with haematological malignancies; removal of exclusion criteria in relationship to patients with pancreatitis; recruitment window extended to 72 hours post development of acute lung injury; definition change of site to include other intensive care units.

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/23419093

http://www.ncbi.nlm.nih.gov/pubmed/28494790

http://www.ncbi.nlm.nih.gov/pubmed/28526233