



## Clinical trial results:

### An efficacy and mechanism evaluation study of Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS)

#### Summary

EudraCT number	2012-005159-18
Trial protocol	GB
Global end of trial date	21 June 2016

#### Results information

Result version number	v1 (current)
This version publication date	10 March 2018
First version publication date	10 March 2018

#### Trial information

##### Trial identification

Sponsor protocol code	CRO2047
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##### Additional study identifiers

ISRCTN number	ISRCTN12776039
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	2nd floor Medical Building, st Mary's Campus, Praed street, London, United Kingdom, W2 1NY
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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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2016
Global end of trial reached?	Yes
Global end of trial date	21 June 2016
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

The main objectives of this trial are:

1. To ascertain if levosimendan reduces the incidence and severity of organ failure as compared to placebo in adult patients who have septic shock.
2. To identify the effect of levosimendan on the function of individual organs function in septic shock.
3. To establish the safety profile and the metabolism of levosimendan by the body in this group of patients.

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Protection of trial subjects:

All patients were treated in an intensive care unit with constant 1:1 nursing care to ensure safety and comfort and minimise any distress.

Background therapy:

Patients were randomised to either treatment group or control group.

The study drug was not started until the treating physician was confident that adequate fluid resuscitation has been achieved and the patient had reached their target mean arterial pressure (suggested target 65-70 mmHg ). Adequate fluid resuscitation was achieved using repeated fluid challenges. Examples of appropriate targets include any or all of the following:

- Central venous pressure  $\geq 8$  mmHg ( $\geq 12$  mmHg in mechanically ventilated patients)
- Good peripheral perfusion on clinical examination
- Other measures of cardiac output / flow, e.g. Stroke Volume Variability (SVV), Global End-Diastolic Volume Index (GEDVI)

Patients received all normal standard care and in addition they received either a 24-hour blinded intravenous infusion of levosimendan or the matched placebo. During the study drug administration and especially during the first 6 hours patients were repeatedly reassessed to ensure adequate fluid resuscitation using any or all of the targets above.

Other management of septic shock including use of inotropes ( e.g. dobutamine) was at the treating physician's discretion, based on the international 'Surviving Sepsis' guidelines. All other drugs was prescribed as clinically indicated.

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Evidence for comparator:

There is a substantial body of research which provides proof of concept that levosimendan improves cardiac output, regional perfusion and other physiological endpoints, including creatinine clearance and glomerular filtration rate in patients who have septic shock. This trial had an exploratory trial design to identify important clinical outcome benefits and to explore the mechanism of action of levosimendan in septic shock. Given that multiple organ dysfunction is associated with an increased mortality, a reduction in the incidence and severity of organ failure would be associated with meaningful benefits to patients and clinicians alike.

Actual start date of recruitment	10 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 515
Worldwide total number of subjects	515
EEA total number of subjects	515

Notes:

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**Subjects enrolled per age group**

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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)	191
From 65 to 84 years	299
85 years and over	25

## Subject disposition

### Recruitment

#### Recruitment details:

This was a double-blind randomised placebo controlled parallel group trial. It was conducted in 34 general adult ICUs within the UK.

Patients were randomised to receive an intravenous infusion of either levosimendan or placebo for the duration of 24hours in addition to standard care.

### Pre-assignment

#### Screening details:

Patients who were clinically judged to have septic shock were screened against the inclusion and exclusion criteria and this required a history and clinical examination. A full blood count or an arterial blood gas samples would be needed but this would be collected as part of their routine clinical care.

### Period 1

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

#### Blinding implementation details:

Vials of levosimendan and matching placebo were supplied by Orion Corporation Orion Pharma, Espoo, Finland. Trial specific labelling and packaging, to ensure trial packs were identical, was undertaken by Victoria Pharmaceuticals, Belfast, UK. Patients, clinical and research staff remained blinded to treatment allocation throughout the trial.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Levosimendan

#### Arm description:

Patients will be randomised to receive an intravenous infusion of either levosimendan (0.05 to 0.2 µg/kg/min) .

The study drug infusion will start at 0.1 µg/kg/min and if tolerated will be increased after 2-4 hours to 0.2 µg/kg/min for the remaining 20-22 hours (maximum 24 hour infusion). If there are subsequent adverse effects the rate of infusion will be reduced back to 0.1 µg/kg/min. If there are adverse effects at an infusion rate of 0.1 µg/kg/min (either initially or later) then the rate of infusion will be reduced to 0.05 µg/kg/min or discontinued.

Arm type	Experimental
Investigational medicinal product name	Levosimendan
Investigational medicinal product code	
Other name	Simdax
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous drip use

#### Dosage and administration details:

The study drug was commenced at a rate of 0.1ug/kg/min and if tolerated was increased after 2-4 hours to 0.2ug/kg/min for a further 20-22 hours. patients received intravenous fluid boluses for ant clinically significant drop in blood pressure and , if ne

<b>Arm title</b>	placebo
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#### Arm description:

Patients will be randomised to receive an intravenous infusion of placebo (0.05 to 0.2 µg/kg/min) for a duration of 24 hours in addition to standard care.

Arm type	Placebo
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Investigational medicinal product name	placebo
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Patients will receive all normal standard care and in addition they will receive a 24-hour blinded intravenous infusion of matching placebo. The placebo infusion rate will follow the treatment group regimen;

infusion will start at 0.1 µg/kg/min and if tolerated will be increased after 2-4 hours to 0.2 µg/kg/min for a further 20-22 hours (total infusion of 24 hours).

<b>Number of subjects in period 1</b>	Levosimendan	placebo
Started	258	257
Completed	255	254
Not completed	3	3
Adverse event, serious fatal	2	2
Physician decision	1	-
Enrolled while trial on temporary halt	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Randomised and included
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Reporting group description: -

Reporting group values	Randomised and included	Total	
Number of subjects	515	515	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	68		
inter-quartile range (Q1-Q3)	58 to 76	-	
Gender categorical			
Units: Subjects			
Female	226	226	
Male	289	289	
Source of infection			
Units: Subjects			
Lung	201	201	
abdomen	191	191	
urine	29	29	
primary bacteremia	10	10	
neurological	5	5	
Soft tissue or line	26	26	
other	52	52	
Missing	1	1	
Mechanical ventilation			
Units: Subjects			
Receiving mechanical ventilation	417	417	
Not receiving mechanical ventilation	98	98	
Renal replacement therapy (RRT)			
Units: Subjects			
Receiving RRT	89	89	
Not receiving RRT	426	426	
Moderate or severe ARDS			
Units: Subjects			

Yes	131	131	
No	384	384	
Ethnicity			
Units: Subjects			
Asian	21	21	
Black	10	10	
White	480	480	
Other	4	4	
History of recent surgery			
Defined as admission to the intensive care unit from the operating room.			
Units: Subjects			
Yes	189	189	
No	326	326	
Beta-blockers normally taken			
Units: Subjects			
Yes	99	99	
No	416	416	
Positive microbiological culture			
Units: Subjects			
Yes	221	221	
No	294	294	
Heart rhythm			
Units: Subjects			
Sinus rhythm	419	419	
Atrial fibrillation	53	53	
Paced	5	5	
Other irregular rhythm	36	36	
Missing	2	2	
Respiratory Failure at Randomisation			
Patients can have failure in more than one organ. Some patients were missing organ failure data at baseline as follows: respiratory - 2 patients; coagulation- 4 patients; hepatic - 11 patients; neurological - 79 patients; renal - 1 patient.			
Units: Subjects			
Respiratory Failure	200	200	
No Respiratory Failure	315	315	
Renal Failure at Randomisation			
Patients can have failure in more than one organ. Some patients were missing organ failure data at baseline as follows: respiratory - 2 patients; coagulation- 4 patients; hepatic - 11 patients; neurological - 79 patients; renal - 1 patient.			
Units: Subjects			
Renal Failure	151	151	
No Renal Failure	364	364	
Hepatic Failure at Randomisation			
Patients can have failure in more than one organ. Some patients were missing organ failure data at baseline as follows: respiratory - 2 patients; coagulation- 4 patients; hepatic - 11 patients; neurological - 79 patients; renal - 1 patient.			
Units: Subjects			
Hepatic Failure	14	14	
No Hepatic Failure	501	501	
Coagulation failure at randomisation			
Patients can have failure in more than one organ. Some patients were missing organ failure data at baseline as follows: respiratory - 2 patients; coagulation- 4 patients; hepatic - 11 patients; neurological - 79 patients; renal - 1 patient.			

Units: Subjects			
coagulation failure	29	29	
No coagulation Failure	486	486	
Neurological failure at randomisation			
Patients can have failure in more than one organ. Some patients were missing organ failure data at baseline as follows: respiratory - 2 patients; coagulation- 4 patients; hepatic - 11 patients; neurological - 79 patients; renal - 1 patient.			
Units: Subjects			
neurological failure	228	228	
No Neurological Failure	287	287	
Pre-existing conditions:Ischemic Heart disease			
One subject can have multiple conditions			
Units: Subjects			
Ischemic heart disease	77	77	
No Ischemic heart disease	438	438	
Pre-existing conditions congestive heart failure			
One subject can have more than one condition			
Units: Subjects			
congestive heart failure	5	5	
No congestive heart failure	510	510	
Pre-exisiting condition: cardiac failure			
one subject can have more than one condition			
Units: Subjects			
cardiac failure	49	49	
No cardiac Failure	466	466	
Pre-exisiting conditions: Severe COPD			
One subject can have more than one condition			
Units: Subjects			
severe COPD	27	27	
No severe COPD	488	488	
Pre-existing conditions: Chronic renal failure			
One subject can have more than 1 condition			
Units: Subjects			
Chronic renal failure	37	37	
No chronic renal failure	478	478	
Pre-existing conditions: Cirrhosis			
One subject may have more than 1 condition			
Units: Subjects			
Cirrhosis	10	10	
No cirrhosis	505	505	
Pre-exisiting condition: Immunocompromised condition			
one subject can have more than 1 condition			
Units: Subjects			
immunocompromised	47	47	
not Immunocompromised	468	468	
Pre-existing condition: diabetes			
one patient may have more than 1 condition			
Units: Subjects			
Diabetes	110	110	



No diabetes	405	405	
Vasoactive drugs at randomisation: Noradrenaline Units: Subjects			
Noradrenaline	508	508	
No Noradrenaline	7	7	
Vasoactive drugs at randomisation: Vasopressin Units: Subjects			
Vasopressin	70	70	
No vasopressin	445	445	
Vasoactive drugs at randomisation : Dobutamine Units: Subjects			
Dobutamine	40	40	
No dobutamine	475	475	
Vasoactive drugs at randomisation: Adrenaline Units: Subjects			
Adrenaline	42	42	
No adrenaline	473	473	
BMI (kg/m2)			
Missing for 9 patients.			
Units: kg/m2			
median	27		
inter-quartile range (Q1-Q3)	23 to 31	-	
APACHE II score			
Acute physiology and chronic health evaluation ( range 0-72, a higher score corresponds to a more severe illness and a higher risk of death)			
Units: number			
median	25		
inter-quartile range (Q1-Q3)	21 to 30	-	
Mean Arterial pressure			
Units: mmHg			
median	74		
inter-quartile range (Q1-Q3)	68 to 79	-	
heart rate			
Units: beats / minute			
median	95		
inter-quartile range (Q1-Q3)	80 to 110	-	
cardiac index			
Units: L/min/m2			
median	3		
inter-quartile range (Q1-Q3)	2.2 to 3.8	-	
Lactate			
Missing for 5 patients.			
Units: mmol/L			
median	2.3		
inter-quartile range (Q1-Q3)	1.4 to 3.6	-	
Time from shock to randomisation			
The onset of shock was defined as the initiation of vasopressors			
Units: hours			
median	16		

inter-quartile range (Q1-Q3)	0 to 21	-	
Noradrenaline dose at randomisation			
Restricted to patients receiving noradrenaline at baseline			
Units: micrograms/kg/hour			
median	0.28		
inter-quartile range (Q1-Q3)	0.16 to 0.47	-	
Adrenaline dose at randomisation			
Restricted to patients receiving adrenaline at randomisation			
Units: micrograms/kg/hour			
median	0.14		
inter-quartile range (Q1-Q3)	0.07 to 0.3	-	
Vasopressin dose at randomisation			
Restricted to patients receiving vasopressin at randomisation			
Units: Units/min			
median	0.03		
inter-quartile range (Q1-Q3)	0.02 to 0.04	-	
Dobutamine dose at randomisation			
Restricted to patients receiving dobutamine at randomisation			
Units: milligram(s)/hour			
median	5.2		
inter-quartile range (Q1-Q3)	4.4 to 6.5	-	
APACHE II score			
Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0-72, with higher scores indicating more severe illness and a higher risk of death.			
Units: none			
median	25		
inter-quartile range (Q1-Q3)	21 to 30	-	
Total SOFA score at randomisation			
Scores on the Sequential Organ Failure Assessment (SOFA) were calculated on the basis of six organ systems (cardiovascular, respiratory, renal, hepatic, coagulation, neurological) at baseline. Note that the neurological score was not included for scores after randomisation.			
Units: none			
median	10		
inter-quartile range (Q1-Q3)	8 to 12	-	
Central venous pressure			
Missing for 143 patients.			
Units: mmHg			
median	11		
inter-quartile range (Q1-Q3)	8 to 15	-	
Arterial oxygen saturation (SaO2)			
Missing for 6 patients.			
Units: percent			
median	97		
inter-quartile range (Q1-Q3)	95 to 98	-	
Central venous oxygen saturation (ScvO2)			
Missing for 172 patients.			
Units: percent			
median	76		
inter-quartile range (Q1-Q3)	69 to 81	-	
PaO2/FiO2 ratio			
Units: kPa			
median	29		

inter-quartile range (Q1-Q3)	20 to 39	-	
Creatinine			
Missing for 2 patients.			
Units: micromole(s)/litre			
median	138		
inter-quartile range (Q1-Q3)	91 to 213	-	
Bilirubin			
Missing for 11 patients.			
Units: micromole(s)/litre			
median	14		
inter-quartile range (Q1-Q3)	8 to 26	-	
Haemoglobin			
Units: gram(s)/litre			
median	108		
inter-quartile range (Q1-Q3)	94 to 124	-	
Platelets			
Missing for 4 patients.			
Units: x 10 <sup>9</sup> per litre			
median	215		
inter-quartile range (Q1-Q3)	140 to 307	-	
Glasgow Coma Scale score			
Scores range from 3 to 15, with lower scores indicating a greater depression of consciousness. Missing for 79 patients.			
Units: none			
median	9		
inter-quartile range (Q1-Q3)	3 to 15	-	

## End points

### End points reporting groups

Reporting group title	Levosimendan
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Reporting group description:

Patients will be randomised to receive an intravenous infusion of either levosimendan (0.05 to 0.2 µg/kg/min) .

The study drug infusion will start at 0.1 µg/kg/min and if tolerated will be increased after 2-4 hours to 0.2 µg/kg/min for the remaining 20-22 hours (maximum 24 hour infusion). If there are subsequent adverse effects the rate of infusion will be reduced back to 0.1 µg/kg/min. If there are adverse effects at an infusion rate of 0.1 µg/kg/min (either initially or later) then the rate of infusion will be reduced to 0.05 µg/kg/min or discontinued.

Reporting group title	placebo
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Reporting group description:

Patients will be randomised to receive an intravenous infusion of placebo (0.05 to 0.2 µg/kg/min) for a duration of 24 hours in addition to standard care.

### Primary: Mean Daily SOFA score

End point title	Mean Daily SOFA score
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End point description:

The mean daily Sequential Organ Failure Assessment (SOFA) score while the patient was in ICU, as measured from randomisation to a maximum of 28 days. The daily score was calculated for each of 5 organ systems (cardiovascular, respiratory, renal, hepatic, and coagulation systems). Component scores range from 0-4 (with higher scores indicating more severe organ dysfunction) giving a maximum total score of 20. For each patient, scores from each day were added together and divided by the number of days to give the mean daily SOFA score.

End point type	Primary
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End point timeframe:

From randomisation to ICU discharge

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: no units				
arithmetic mean (standard deviation)	6.68 (± 3.96)	6.06 (± 3.89)		

### Statistical analyses

Statistical analysis title	Mean difference (bootstrap CI)
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Statistical analysis description:

The absolute mean difference (levosimendan - placebo) with a 95% confidence interval calculated using bootstrap methods.

Comparison groups	Levosimendan v placebo
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Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	1.29

<b>Statistical analysis title</b>	Adjusted mean difference
Statistical analysis description:	
Mean difference in SOFA score comparing levosimendan and placebo from regression analysis, adjusting for age, baseline APACHE II score and allowing for clustering by ICU.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	1.2

<b>Primary: Respiratory SOFA score</b>	
End point title	Respiratory SOFA score
End point description:	
End point type	Primary
End point timeframe:	
From randomisation to ICU discharge up to a maximum of 28 days	

<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	1.7 (± 1.18)	1.56 (± 1.15)		

## Statistical analyses

Statistical analysis title	Mean difference (bootstrap CI)
Statistical analysis description: Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.34

## Primary: Coagulation SOFA score

End point title	Coagulation SOFA score
End point description:	
End point type	Primary
End point timeframe: From randomisation to ICU discharge up to a maximum of 28 days	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	0.75 ( $\pm$ 1.05)	0.75 ( $\pm$ 1.02)		

## Statistical analyses

Statistical analysis title	Mean difference (bootstrap CI)
Statistical analysis description: Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo

Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.17

### Primary: Hepatic SOFA score

End point title	Hepatic SOFA score
End point description:	
End point type	Primary
End point timeframe:	
From randomisation to ICU discharge up to a maximum of 28 days	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	0.51 ( $\pm$ 0.84)	0.45 ( $\pm$ 0.77)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean difference (bootstrap CI)
Statistical analysis description:	
Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.19

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**Primary: Cardiovascular SOFA score**

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End point title	Cardiovascular SOFA score
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End point description:

End point type	Primary
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End point timeframe:

From randomisation to ICU discharge up to a maximum of 28 days

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End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	2.27 (± 1.2)	2.02 (± 1.2)		

**Statistical analyses**

Statistical analysis title	Mean difference (bootstrap CI)
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Statistical analysis description:

Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.

Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.46

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**Primary: Renal SOFA score**

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End point title	Renal SOFA score
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End point description:

End point type	Primary
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End point timeframe:

From randomisation to ICU discharge up to a maximum of 28 days

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<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	1.46 ( $\pm$ 1.49)	1.28 ( $\pm$ 1.38)		

## Statistical analyses

<b>Statistical analysis title</b>	Mean difference (bootstrap CI)
Statistical analysis description:	
Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.42

## Primary: Mean daily SOFA score - excluding cardiovascular

End point title	Mean daily SOFA score - excluding cardiovascular
End point description:	
Sensitivity analysis for primary outcome excluding the cardiovascular component.	
End point type	Primary
End point timeframe:	
From randomisation to ICU discharge up to a maximum of 28 days	

<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	4.41 ( $\pm$ 3.13)	4.05 ( $\pm$ 3.07)		

## Statistical analyses

<b>Statistical analysis title</b>	Mean difference (bootstrap CI)
Statistical analysis description: Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.9

## Primary: Mean SOFA score - sensitivity analysis

End point title	Mean SOFA score - sensitivity analysis
End point description: Sensitivity analysis using Bayesian methods to impute the missing data rather than the last observation carried forward approach taken in the main analysis.	
End point type	Primary
End point timeframe: From randomisation to ICU discharge up to a maximum of 28 days	

<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: none				
arithmetic mean (standard deviation)	7.19 ( $\pm$ 3.72)	6.78 ( $\pm$ 3.74)		

## Statistical analyses

<b>Statistical analysis title</b>	Mean difference (bootstrap CI)
Statistical analysis description: Absolute difference in means comparing levosimendan and placebo with bootstrapped confidence	

interval.

Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.06

### Secondary: 28 day mortality

End point title	28 day mortality
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to 28 days	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256 <sup>[1]</sup>		
Units: Number of patients				
Died	89	79		

Notes:

[1] - One patient declined follow up after ICU discharge but before day 28

<b>Attachments (see zip file)</b>	Kaplan Meier plot of survival to 28 days/tt_death_km.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Absolute difference in proportions
Comparison groups	placebo v Levosimendan
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	11.7

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**Secondary: Mortality at ICU discharge**

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End point title	Mortality at ICU discharge
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to ICU discharge

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End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: Number of patients				
Died	83	76		

**Statistical analyses**

<b>Statistical analysis title</b>	Absolute difference in proportions
Comparison groups	placebo v Levosimendan
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	10.6

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**Secondary: number of catecholamine free days**

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End point title	number of catecholamine free days
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End point description:

Days free of any catecholamine therapy (noradrenaline, adrenaline and dobutamine). There were no patients with 28 days free of catecholamine therapy as this was an inclusion criterion to enter the trial.

End point type	Secondary
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End point timeframe:

From randomisation to 28 days.

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End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256 <sup>[2]</sup>		
Units: days				
median (inter-quartile range (Q1-Q3))	22 (0 to 26)	23 (0 to 26)		

Notes:

[2] - One patient withdrew consent after ICU discharge but before day 28

## Statistical analyses

Statistical analysis title	Absolute difference in medians
Statistical analysis description:	
Absolute difference in medians calculated using bootstrapping.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	1

## Secondary: Number of ventilation free days

End point title	Number of ventilation free days
End point description:	
0 for patients that died before extubation; 28 less the number of ventilation days for patients surviving to day 28; days to death less ventilation days for subjects dead at day 28 but after extubation. For subjects discharged from ICU before 28 days whilst ventilated, days between ICU discharge and successful weaning from ventilation were counted as ventilation days.	
End point type	Secondary
End point timeframe:	
From randomisation to 28 days	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256 <sup>[3]</sup>	253 <sup>[4]</sup>		
Units: days				
median (inter-quartile range (Q1-Q3))	16 (0 to 25)	19 (0 to 25)		

Notes:

[3] - 2 patients had missing data as they were transferred ventilated before 28 days.

[4] - Four patients excluded due to missing data on weaning from ventilation.

## Statistical analyses

<b>Statistical analysis title</b>	Absolute difference in medians
Statistical analysis description: Absolute difference in medians with bootstrap confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	1

## Secondary: Major acute kidney event over 28 days

End point title	Major acute kidney event over 28 days
End point description: Patients were defined as having MAKE28 if they died, required renal replacement therapy (RRT) before day 28, or had prolonged renal failure defined as AKI stage 2 or 3 at day 28 (or at ICU discharge if discharged before day 28).	
End point type	Secondary
End point timeframe: From randomisation to day 28	

<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256 <sup>[5]</sup>		
Units: number of patients				
MAKE28	148	139		

Notes:

[5] - One patient withdrew consent after ICU discharge but before day 28

## Statistical analyses

<b>Statistical analysis title</b>	Absolute difference in proportions
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Statistical analysis description:

Absolute difference in proportions comparing levosimendan with placebo.

Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	11.6

## Secondary: Mortality at hospital discharge

End point title	Mortality at hospital discharge
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation until hospital discharge	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256 <sup>[6]</sup>		
Units: number of patients				
Died	97	84		

Notes:

[6] - One patient withdrew consent after ICU discharge but before day 28

## Statistical analyses

<b>Statistical analysis title</b>	Absolute difference in proportions
Statistical analysis description:	
Absolute difference in proportions comparing levosimendan with placebo.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	13

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**Secondary: need for new renal replacement therapy**

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End point title	need for new renal replacement therapy
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to day 28

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End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257 <sup>[7]</sup>	257		
Units: Number of patients				
RRT	62	62		

Notes:

[7] - One patient with missing data

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**Statistical analyses**

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Statistical analysis title	Absolute difference in proportions
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	7.4

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**Secondary: Time to extubation**

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End point title	Time to extubation
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End point description:

Time to extubation in days. All patients were censored at 28 days and deaths were treated as still ventilated at the end of follow up. Patients who were not ventilated at baseline or day 1 were excluded.

End point type	Secondary
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End point timeframe:

From randomisation to extubation, up to a maximum of 28 days.

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<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215 <sup>[8]</sup>	218 <sup>[9]</sup>		
Units: Number of patients				
Number extubated by day 28	127	150		

Notes:

[8] - Restricted to patients ventilated on baseline or day 1.

[9] - Restricted to patients ventilated at baseline or day 1.

<b>Attachments (see zip file)</b>	Kaplan Meier plot of time to extubation/tt_extub_km_new.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Cox regression
Statistical analysis description:	
Cox regression comparing time to extubation in Levosimendan and Placebo.	
Comparison groups	placebo v Levosimendan
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.99

## Secondary: Sustained renal failure

End point title	Sustained renal failure
End point description:	
Sustained renal failure at day 28, or at ICU discharge if before 28 days.	
End point type	Secondary
End point timeframe:	
Day 28, or at ICU discharge if before 28 days.	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: Patients				
Sustained renal failure	118	108		

## Statistical analyses

Statistical analysis title	Absolute difference in proportions
Statistical analysis description:	
Absolute difference in proportions comparing Levosimendan and placebo	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	12.3

## Secondary: Length of ICU stay

End point title	Length of ICU stay
End point description:	
End point type	Secondary
End point timeframe:	
From ICU admission to ICU discharge	

End point values	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: days				
median (inter-quartile range (Q1-Q3))	7.3 (3.2 to 14.8)	8.3 (3.9 to 13.5)		

## Statistical analyses

<b>Statistical analysis title</b>	Median difference (bootstrap CI)
Statistical analysis description: Absolute difference in medians comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.8

### Secondary: Length of hospital stay

End point title	Length of hospital stay
End point description:	
End point type	Secondary
End point timeframe:	
From hospital admission to hospital discharge	

<b>End point values</b>	Levosimendan	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	257		
Units: days				
median (inter-quartile range (Q1-Q3))	19.6 (10.1 to 40.4)	22.7 (11.7 to 42.3)		

### Statistical analyses

<b>Statistical analysis title</b>	Median difference (bootstrap CI)
Statistical analysis description: Absolute difference in medians comparing levosimendan and placebo with bootstrapped confidence interval.	
Comparison groups	Levosimendan v placebo

Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	2.2

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Serious Adverse Events should be reported within 24 hours. Fatal or life threatening SAEs should be reported on the day that the local site is aware of the event.

Adverse event reporting additional description:

clinical outcomes from sepsis are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of the study drug

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Levosimendan
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

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: As all patients included in the trial were critically ill, by definition, it is very difficult to define what is an adverse event as they will all have abnormal blood results and physiological signs as part of their underlying illness. Therefore the trial focused only on serious adverse events, as the priority safety analysis.

Serious adverse events	Levosimendan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 255 (12.55%)	23 / 253 (9.09%)	
number of deaths (all causes)	10	9	
number of deaths resulting from adverse events	0	0	
Investigations			
investigations			
subjects affected / exposed	1 / 255 (0.39%)	0 / 253 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
vascular disorder			
subjects affected / exposed	7 / 255 (2.75%)	4 / 253 (1.58%)	
occurrences causally related to treatment / all	1 / 7	1 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac disorders			
atrial fibrillation / supraventricular tachycardia			

subjects affected / exposed	8 / 255 (3.14%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	2 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 255 (0.00%)	2 / 253 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
ventricular fibrillation / tachycardia			
subjects affected / exposed	7 / 255 (2.75%)	3 / 253 (1.19%)	
occurrences causally related to treatment / all	7 / 7	1 / 3	
deaths causally related to treatment / all	2 / 2	0 / 1	
Myocardial infarction / acute coronary syndrome			
subjects affected / exposed	3 / 255 (1.18%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	2 / 255 (0.78%)	1 / 253 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	4 / 255 (1.57%)	7 / 253 (2.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	4 / 255 (1.57%)	5 / 253 (1.98%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Levosimendan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 255 (0.00%)	0 / 253 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2013	<ul style="list-style-type: none"> <li>•Addition of 3 new investigational sites, Nottingham University Hospitals NHS Trust (PI is Dan Harvey), Western Health and Social Care Trust, Northern Ireland (PI is Noel Hemmings) and Northern Health and Social Care Trust, Northern Ireland (PI is Christopher Nutt)</li> <li>•Change in the name of Principal Investigator at 3 participating investigational sites South Tees Hospitals NHS Foundation Trust (PI change from Judith Wright to Jost Mullenheim) York Teaching Hospitals NHS Foundation Trust (PI change from David Yates to John Berridge) Belfast Health and Social Care Trust (PI change from Danny McAuley to James McNamee)</li> </ul>
18 November 2013	<p>Change in the name of Principal Investigator at 3 participating investigational sites:</p> <ol style="list-style-type: none"> <li>1.Norfolk and Norwich University Hospitals NHS Foundation Trust (PI change from Simon Fletcher to Jurgens Nortje)</li> <li>2.Queen Elizabeth Hospital, Kings Lynn, NHS Foundation Trust (PI change from Mark Blunt to Darcy Pearson)</li> <li>3.James Paget University Hospitals NHS Foundation Trust (PI change from Pieter Bothma to Hazel Stuart)</li> </ol>
28 July 2014	Temporary halt of recruitment. Recruitment was temporarily halted by the Sponsor due to some mould being found on the secondary packaging of some IMP kits.
18 August 2014	Re-start of Patient Recruitment. The IMP has been recalled, effected kits destroyed and other packs reworked and now released for trial use.
05 September 2014	<p>Addition of 10 new investigational sites:</p> <ol style="list-style-type: none"> <li>1.Royal Sussex County Hospital, Brighton and Sussex University Hospitals NHS Trust; PI: Dr Stephen Drage</li> <li>2.Frenchay Hospital Bristol, North Bristol NHS Trust; PI: Dr Matt Thomas</li> <li>3.Countess of Chester Hospital NHS Trust; PI: Dr Nicole Robin</li> <li>4.Medway Maritime Hospital, Medway NHS Foundation Trust; PI: Dr Nandita Divekar</li> <li>5.Ipswich Hospital NHS Trust; PI: Dr Richard Howard-Griffin</li> <li>6.Kettering General Hospital NHS Foundation Trust; PI: Dr Philip Watt</li> <li>7.Leicester Royal Infirmary, University Hospital of Leicester NHS Trust; PI: Dr Simon Scott</li> <li>8.Royal Free Hospital, Royal Free London NHS Foundation Trust; PI: Dr Daniel Martin</li> <li>9.Salford Royal NHS Foundation Trust; PI: Dr Paul Dark</li> <li>10.Pinderfields Hospital, The Mid Yorkshire Hospital NHS Trust; PI: Dr Alastair Rose</li> </ol>



08 October 2014	<p>Change of 2 Principal Investigators at participating study sites:</p> <p>1.Countess of Chester Hospital NHS Trust; New PI: Dr Peter Turton (previously: Dr Nicole Robin)</p> <p>2.Salford Royal NHS Foundation Trust; New PI: Dr Justin Roberts (previously Dr Paul Dark)</p>
12 January 2015	<p>Change of 1 Principal Investigators at participating study site:</p> <p>1.University Hospital of North Midlands NHS Trust (formerly University Hospital of North Staffordshire NHS Trust); New PI: Dr Nicholas Coleman (previously: Dr Kumaresh Venkatesan)</p>
06 May 2015	<p>The trial protocol was updated to version 1.1 due to the addition of a tertiary exploratory outcome measure in the form of an echocardiographic sub-study. We also performed some minor corrections and clarifications.</p> <p>In line with the above amendment we also added a sentence to the patient information sheet and updated this to v1.4. The additional wording is: "In some hospitals we are also carrying out ultrasound scans of the heart on three occasions in the intensive care unit to examine the effect of levosimendan on heart function. This is a routine examination in these hospitals and will only involve placing an ultrasound probe with some jelly on your chest."</p> <p>The echocardiographic sub-study was discussed with the Trial Management Group and the Trial Steering Committee with patient and public representation.</p>
06 May 2015	<p>Change of 1 Principal Investigator at a participating study site:</p> <p>1.Countess of Chester Hospital NHS Trust; New PI: Dr Simon Ridler (previously: Dr Peter Turton)</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 July 2014	Recruitment was temporarily halted by the Sponsor due to some mould being found on the secondary packaging of some IMP kits. The IMP has been recalled, effected kits destroyed and other packs reworked and now released for trial use. REC approval for restart of the trial was received on 26/08/14 and MHRA approval for restart of the trial was received on 08/09/14. The 1st patient after the halt, was recruited on 15/09/14 and recruitment remained unaffected for the remainder of the trial.	08 September 2014

Notes:

## Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27705084>