Clinical trial results:
Adjunctive Rifampicin to Reduce Early mortality from Staphylococcus aureus bacteraemia: a randomised controlled trial

Summary

EudraCT number	2012-000344-10
Trial protocol	GB
Global end of trial date	18 January 2017

Results information

Result version number	v1 (current)
This version publication date	31 January 2018
First version publication date	31 January 2018

Trial information

Trial identification

Sponsor protocol code	ARREST

Additional study identifiers

ISRCTN number	ISRCTN37666216
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	90 High Holborn, 2nd Floor, London, United Kingdom, WC1V 6LJ
Public contact	Professor A Sarah Walker, MRC Clinical Trials Unit at UCL, 44 2076704726, rmjlasw@ucl.ac.uk
Scientific contact	Professor A Sarah Walker, MRC Clinical Trials Unit at UCL, 44 2076704726, rmjlasw@ucl.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	20 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2017
Global end of trial reached?	Yes
Global end of trial date	18 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the addition of 14 days rifampicin to initial standard antibiotic therapy reduce bacteriological failure/death through 12 weeks from randomisation in adults with Staphylococcus aureus bacteraemia?

Protection of trial subjects:

A Data Monitoring Committee (DMC) was established. The DMC could recommend premature closure or reporting of the trial, or that recruitment be discontinued or modified.

Background therapy:

Despite scant data from controlled trials, current treatment guidelines recommend that S. aureus bacteraemia should be treated with at least 14 days of an intravenous (IV) beta-lactam antibiotic, or a glycopeptide if the bacteria are meticillin-resistant. Combination antimicrobial therapy is generally not recommended, except in severe meticillin-resistant S. aureus (MRSA) infections (e.g. endocarditis, prosthetic joint infections). Most of the recommendations are based on uncontrolled observational studies and clinical experience, and views of how to manage S. aureus bacteraemia differ widely.

To estimate the degree of uncertainty around clinical practice within the NHS we conducted a multi-centre, prospective observational study of patients with S. aureus bacteraemia. The findings from the first year (November 2008-2009; 549 cases) revealed that management varied widely among NHS Trusts, with little adherence to the published guidelines. Centres varied significantly ($p<0.01$) in the proportions given oral treatment alone for >50% of treatment (range 12-40% across NHS Trusts), in those treated for longer than 28 days (range 13-54%), and in those given combination antimicrobial therapy (range 14-94%). Twenty four percent of patients died during admission, 72% within the first 14 days of treatment. Older age, longer time in hospital before bacteraemia, and an unidentified infection focus were independent predictors of in-hospital death ($p<0.001$).

Our literature review and observational study confirm S. aureus to be a common, frequently fatal blood infection within NHS Hospitals - yet the optimal management remains uncertain and practice highly variable. In particular, key questions concerning the most effective antimicrobial regimen are unanswered, and will remain so until they have been addressed by large, well-conducted RCTs. For reasons described below, one major clinical research priority is to assess the role of adjuvant antibiotic therapy.

Evidence for comparator:

Three properties make rifampicin an attractive, if unproven, antibiotic for S. aureus bacteraemia treatment. First, it has good oral bioavailability. Second, it penetrates cells, tissues, and biofilms better than beta-lactam and glycopeptide antibiotics (the current mainstays of S. aureus bacteraemia treatment) and, therefore, in combination with these agents, may resolve serious S. aureus infections faster and more effectively. And third, it is cheap: a daily 600mg dose costs £0.73 by mouth and £7.67 intravenously.

There are three important potential problems with using rifampicin for the treatment of S. aureus bacteraemia: the development of rifampicin resistant bacteria, interactions with other drugs, and hepatic toxicity. Resistance can be acquired rapidly when rifampicin is used alone in treatment, resulting from mutations in the drug’s binding site (the β-subunit of the bacterial DNA-dependent RNA polymerase). Interactions with other drugs are mediated by rifampicin’s ability to increase their metabolism through the potent induction of the hepatic cytochrome p450 system. Lastly, rifampicin can cause hepatic toxicity, although the enormous worldwide experience of using rifampicin for the prevention and 6-month treatment of tuberculosis confirms the drug is extremely well-tolerated and causes clinically significant hepatitis in <1% of patients.

Actual start date of recruitment	10 December 2012
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: 758
Worldwide total number of subjects	758
EEA total number of subjects	758

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)	376
From 65 to 84 years	313
85 years and over	69

Subject disposition

Recruitment

Recruitment details:

Adults (≥18 years) were recruited from 29 hospitals from around the United Kingdom. Subjects were recruited by the study team and in consultation with the hospital team responsible for the patient's in-hospital care. Subjects, or their legal representatives (in the case of incapacity), gave written informed consent. Main eligibility criteria below.

Pre-assignment

Screening details:

INCLUSION CRITERIA
S aureus (meticillin-susceptible/resistant) grown from ≥1 blood culture
<96h active antibiotic therapy for current infection, not including rifampicin
EXCLUSION CRITERIA
Infection not caused by S aureus alone
Sensitivity results already available and demonstrate rifampicin resistant S aureus
Rifampicin contraindicated
TB

Pre-assignment period milestones

Number of subjects started	2884[1]
Number of subjects completed	758

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Non-randomisation: 2126

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2884 subjects were screened, but 758 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, Carer, Assessor

Blinding implementation details:

Rifampicin can turn urine orange-red. This is variable both within and between subjects, but a potential source of unblinding, particularly of subjects. The opportunity for doctors/nurses to examine urine at the bedside only occurred in subjects with catheters, removed at the earliest opportunity.

Rifampicin capsules were overencapsulated to make them indistinguishable from placebo. In those needing IV treatment, pharmacists dispensed rifampicin for infusion or saline, with an opaque cover.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Treatment with placebo for 14 days from randomisation (oral and/or IV according to patient status) (plus standard backbone
antibiotic therapy as chosen by the physician):

Placebo oral 300 mg capsules containing cellulose
Standard saline for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is always given intravenously.

The dose of placebo was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
those ≥60kg received 900mg every 24h

Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm). The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case placebo was given until standard antibiotic treatment ended.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Placebo was given by oral or intravenous route, according to the attending physician's preference and the patient's status. Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is always given intravenously. Patients may start taking IV placebo and then move to the oral formulation when they could swallow safely. We anticipated around 90% of doses would be given by mouth.

Arm title	Rifampicin

Arm description:

Active treatment with rifampicin for 14 days from randomisation (oral and/or IV according to patient status) (plus standard antibiotic):

Rifampicin oral 300 mg capsules
Rifampicin 600 mg for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy is always given intravenously.

The dose of rifampicin was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
those ≥60kg received 900mg every 24h

Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this provided adequate exposure. The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case rifampicin was given until standard antibiotic treatment ended.

Arm type	Experimental
Investigational medicinal product name	Rifampicin
Investigational medicinal product code	
Other name	Rifampin
Pharmaceutical forms	Capsule, Powder for concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Rifampicin was given by oral or intravenous route, according to the attending physician's preference and the patient's status. Oral rifampicin has excellent bioavailabilty with oral administration achieving comparable plasma concentrations to the intravenous route. Therefore, provided a patient can swallow safely, most physicians will elect to use rifampicin orally. We anticipated around 90% of doses would be given by mouth. Patients may start taking IV rifampicin and then move to the oral formulation when they could swallow safely.

It is important, however, to allow intravenous administration to very sick patients who may not be able to swallow or absorb tablets. Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is always given intravenously.

Number of subjects in period 1	Placebo	Rifampicin
Started	388	370
Completed	360	333
Not completed	28	37
Consent withdrawn by subject	7	15
Lost to follow-up	21	22

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Treatment with placebo for 14 days from randomisation (oral and/or IV according to patient status) (plus standard backbone
antibiotic therapy as chosen by the physician):

Placebo oral 300 mg capsules containing cellulose
Standard saline for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is always given intravenously.

The dose of placebo was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
those ≥60kg received 900mg every 24h

Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm). The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case placebo was given until standard antibiotic treatment ended.

Reporting group title	Rifampicin

Reporting group description:

Active treatment with rifampicin for 14 days from randomisation (oral and/or IV according to patient status) (plus standard antibiotic):

Rifampicin oral 300 mg capsules
Rifampicin 600 mg for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy is always given intravenously.

The dose of rifampicin was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
those ≥60kg received 900mg every 24h

Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this provided adequate exposure. The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case rifampicin was given until standard antibiotic treatment ended.

Reporting group values	Placebo	Rifampicin	Total
Number of subjects	388	370	758
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)	185	191	376

From 65-84 years	166	147	313
85 years and over	37	32	69

Age continuous			
Units: years			
median	66	64	
inter-quartile range (Q1-Q3)	51 to 76	49 to 76	-
Gender categorical			
Units: Subjects			
Female	142	121	263
Male	246	249	495
Mode of acquisition of infection			
Units: Subjects			
Community acquired	240	245	485
Nosocomial infection (onset >=48h after admission)	76	56	132
Healthcare associated (all other)	72	68	140
Not recorded	0	1	1
Was the patient admitted to ITU before enrolment?			
Units: Subjects			
No	352	335	687
Yes	36	34	70
Not recorded	0	1	1
Was the patient transferred from another hospital?			
Units: Subjects			
No	358	343	701
Yes - date known	30	26	56
Yes - date not known	0	1	1
S. aureus isolated from blood within the 12 weeks preceding this episode			
Units: Subjects			
No	364	355	719
Yes	5	5	10
Not recorded	19	10	29
Intention to give IV study drug			
Units: Subjects			
No	325	305	630
Yes	63	64	127
Not recorded	0	1	1
Likely portal of entry			
Incorporating any changes of opinion of the Infectious Diseases physician since Day 0. Although this includes post-baseline information, the most meaningful categorisation is the one closest to the truth and this includes some post-baseline information			
Units: Subjects			
Skin/soft tissue infection unrelated to surgery	131	124	255
Infected surgical wound within last 3 months	19	19	38
Peripheral vascular catheter (inc. arterial line)	23	26	49
Central vascular catheter (including PICC line)	50	42	92

Other implanted vascular device	15	12	27
Respiratory	16	13	29
Per-urethral urinary catheter	6	6	12
Supra-pubic urinary catheter	1	2	3
Urological surgery within 1 week of bacteraemia	1	3	4
Not known (absence of any of the above)	110	108	218
Other	14	14	28
Not recorded	2	1	3
Active intravenous drug use Units: Subjects			
No	342	326	668
Yes	41	42	83
Not recorded	5	2	7
End stage renal disease having peritoneal dialysis Units: Subjects			
No	384	368	752
Yes	4	1	5
Not recorded	0	1	1
End stage renal disease having haemodialysis Units: Subjects			
No	347	336	683
Yes	40	33	73
Not recorded	1	1	2
Systemic corticosteroid therapy Units: Subjects			
No	381	363	744
Yes	6	5	11
Not recorded	1	2	3
Neutropenia Units: Subjects			
No	381	362	743
Yes	6	7	13
Not recorded	1	1	2
Currently receiving anti-neoplastic chemotherapy Units: Subjects			
No	374	349	723
Yes	14	20	34
Not recorded	0	1	1
Any other immune suppressive therapy? Units: Subjects			
No	362	352	714
Yes	22	17	39
Not recorded	4	1	5
Organ or marrow transplant Units: Subjects			
No	381	362	743
Yes	7	6	13
Not recorded	0	2	2

Any surgery in 30 days before blood culture? Units: Subjects			
No	335	331	666
Yes	53	37	90
Not recorded	0	2	2
Vascular catheter in situ at time of bacteraemia? Units: Subjects			
No	278	275	553
Yes	102	89	191
Not recorded	8	6	14
BMI			
Not recorded for 11 placebo subjects, 10 rifampicin.			
Units: kilogram(s)/square meter			
median	26.4	26.3	
inter-quartile range (Q1-Q3)	22.6 to 31.2	22.5 to 30.7	-
Time between drawing of first positive blood culture and randomisation Units: day			
median	3.0	3.0	
inter-quartile range (Q1-Q3)	2.0 to 3.0	2.0 to 4.0	-
Number of days between admission to current hospital and randomisation Units: day			
median	3.0	3.0	
inter-quartile range (Q1-Q3)	3.0 to 6.0	2.0 to 5.0	-
Time between first new symptom caused by S. aureus and randomisation			
Not recorded for 1 placebo subject, 3 rifampicin.			
Units: day			
median	4.0	4.0	
inter-quartile range (Q1-Q3)	3.0 to 6.0	3.0 to 6.0	-
CRP measured closest to first positive culture			
Mean (standard deviation) estimated using normal interval regression to account for values above limit of quantification in one centre (that is, CRP only reported as >156 mg/L if above this threshold). Not recorded for 2 placebo subjects.			
Units: milligram(s)/litre			
arithmetic mean	173	167	
standard deviation	± 111.5	± 103.8	-
White cell count measured closest to first positive culture			
Not recorded for 3 placebo subjects, 1 rifampicin.			
Units: 10^9/L			
median	10.1	9.9	
inter-quartile range (Q1-Q3)	7.1 to 14.2	7.3 to 14.3	-
Neutrophil count measured closest to first positive culture			
Not recorded for 5 placebo subjects.			
Units: 10^9/L			
median	8.2	7.9	
inter-quartile range (Q1-Q3)	5.1 to 12.0	5.4 to 12.2	-
Lymphocyte count measured closest to			

first positive culture			
Not recorded for 5 placebo subjects, 1 rifampicin.			
Units: 10^9/L			
median	1.0	0.8	
inter-quartile range (Q1-Q3)	0.6 to 1.4	0.6 to 1.3	-
CRP at randomisation			
Mean (standard deviation) estimated using normal interval regression to account for values above limit of quantification in one centre (that is, CRP only reported as >156 mg/L if above this threshold). Not recorded for 2 placebo subjects, 1 rifampicin.			
Units: milligram(s)/litre			
arithmetic mean	163	166	
standard deviation	± 101.9	± 101.2	-
White cell count at randomisation			
Not recorded for 3 placebo subjects, 3 rifampicin.			
Units: 10^9/L			
median	9.5	9.5	
inter-quartile range (Q1-Q3)	6.7 to 13.4	7.1 to 13.1	-
Neutrophil count at randomisation			
Not recorded for 5 placebo subjects, 1 rifampicin.			
Units: 10^9/L			
median	7.3	7.4	
inter-quartile range (Q1-Q3)	4.7 to 11.0	4.9 to 10.7	-
Lymphocyte count at randomisation			
Not recorded for 5 placebo subjects, 2 rifampicin.			
Units: 10^9/L			
median	1.0	1.0	
inter-quartile range (Q1-Q3)	0.7 to 1.5	0.7 to 1.5	-
Charlson comorbidity index score			
Not recorded for 1 rifampicin subject.			
Units: Charlson comorbidity index score			
median	2	1	
inter-quartile range (Q1-Q3)	0 to 3	0 to 3	-
Sepsis related organ failure assessment (SOFA) score			
Not recorded for 68 placebo subjects, 50 rifampicin.			
Units: SOFA score			
median	2.0	2.0	
inter-quartile range (Q1-Q3)	1.0 to 4.0	1.0 to 4.0	-
Days between first new symptom caused by S. aureus and starting active antibiotics			
Not recorded for 1 placebo subject, 3 rifampicin.			
Units: day			
median	1	1	
inter-quartile range (Q1-Q3)	0 to 3	0 to 3	-
Duration of active antibiotic therapy before randomisation Units: day			
median	2.6	2.5	
inter-quartile range (Q1-Q3)	1.8 to 3.1	1.7 to 3.2	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Treatment with placebo for 14 days from randomisation (oral and/or IV according to patient status) (plus standard backbone
antibiotic therapy as chosen by the physician):

Placebo oral 300 mg capsules containing cellulose
Standard saline for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is always given intravenously.

The dose of placebo was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
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Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm). The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case placebo was given until standard antibiotic treatment ended.

Reporting group title	Rifampicin

Reporting group description:

Active treatment with rifampicin for 14 days from randomisation (oral and/or IV according to patient status) (plus standard antibiotic):

Rifampicin oral 300 mg capsules
Rifampicin 600 mg for intravenous injection

Additional intravenous catheters were not required to administer the study drug as standard antibiotic therapy is always given intravenously.

The dose of rifampicin was prescribed according to the patient's weight:

those <60kg received 600mg every 24h
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Oral doses could be given once or twice daily, according to clinician and patient preference. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this provided adequate exposure. The study treatment was given for 14 days, unless fewer than 14 days of standard antibiotic therapy was planned, in which case rifampicin was given until standard antibiotic treatment ended.

Primary: Bacteriological failure

End point title	Bacteriological failure

End point description:

In the protocol, bacteriological failure is defined as death or microbiologically confirmed treatment failure or disease recurrence.

Microbiologically confirmed treatment failure is defined as symptoms and signs of infection for longer than 14 days from randomisation with the isolation of the same strain of S. aureus (confirmed by genotyping) from a sterile site. Disease recurrence is defined as the isolation of the same strain of S. aureus from a sterile site after at least 7 days of apparent clinical improvement. The same strain will be defined as one with the same genotype by multi-locus sequence and spa-typing.

Because of failure to locate bacteriological isolates/missing samples, the primary analysis of the primary endpoint includes all bacteriological failures/recurrences confirmed by the Endpoint Review Committee and a secondary analysis counts as events only those with samples and the same genotype by whole

genome sequencing and spa-typing (or who died).

End point type	Primary

End point timeframe:

Up to 12 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Died without suffering bacteriological failure	50	55		
Suffered bacteriological failure	21	7		

Attachments (see zip file)	Kaplan-Meier curves/anstatus2_new.png

Statistical analyses

Statistical analysis title	Logrank test (unstratified) (primary analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Logrank

Statistical analysis title	Logrank test (stratified by site) (2ndry analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Logrank

Statistical analysis title	Cox model (unstratified) (primary analysis)

Statistical analysis description:

Hazard ratio is for Rifampicin v Placebo (i.e. a hazard ratio of more than one implies a greater hazard in the Rifampicin group).

Comparison groups	Placebo v Rifampicin

Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.35

Statistical analysis title	Cox model (stratified by site) (2ndry analysis)
Statistical analysis description:	
Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Rifampicin v Placebo
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.34

Statistical analysis title	Logrank test (unstratified) (sensitivity analysis)
Statistical analysis description:	
Counting as events only those with samples and the same genotype by whole genome sequencing and spa-typing (or who died).	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Logrank

Statistical analysis title	Logrank test (stratified by site) (sensitivity)
Statistical analysis description:	
Counting as events only those with samples and the same genotype by whole genome sequencing and	

spa-typing (or who died).

Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Logrank

Statistical analysis title	Cox model (unstratified) (sensitivity analysis)

Statistical analysis description:

Counting as events only those with samples and the same genotype by whole genome sequencing and spa-typing (or who died).

Hazard ratio is for Rifampicin v Placebo.

Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.5

Statistical analysis title	Cox model (stratified by site) (sensitivity)

Statistical analysis description:

Counting as events only those with samples and the same genotype by whole genome sequencing and spa-typing (or who died).

Hazard ratio is for Rifampicin v Placebo.

Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.48

Secondary: All-cause mortality to 2 weeks	
End point title	All-cause mortality to 2 weeks
End point description:	

End point type	Secondary
End point timeframe:	
Up to 2 weeks from randomisation.	

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
All-cause mortality to 2 weeks	17	25		

Statistical analyses

Statistical analysis title	Logrank test (unstratified) (primary analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank

Statistical analysis title	Logrank test (stratified by site) (2ndry analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Logrank

Statistical analysis title	Cox model (unstratified) (primary analysis)
Statistical analysis description:	
Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin

Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.95

Statistical analysis title	Cox model (stratified by site) (2ndry analysis)
Statistical analysis description: Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.82

Secondary: All-cause mortality to 12 weeks	
End point title	All-cause mortality to 12 weeks
End point description:	

End point type	Secondary
End point timeframe: Up to 12 weeks from randomisation.	

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
All-cause mortality to 12 weeks	56	56		

Attachments (see zip file)	Kaplan-Meier curves/anstatus.png

Statistical analyses

Statistical analysis title	Logrank test (unstratified) (primary analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Logrank

Statistical analysis title	Logrank test (stratified by site) (2ndry analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Logrank

Statistical analysis title	Cox model (unstratified) (primary analysis)
Statistical analysis description: Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.6

Statistical analysis title	Cox model (stratified by site) (2ndry analysis)
Statistical analysis description: Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.53

Secondary: Clinical failure

End point title	Clinical failure
End point description: Clinical failure is defined as death, treatment failure or disease recurrence (whether or not microbiologically confirmed).	
End point type	Secondary
End point timeframe: Up to 12 weeks from randomisation.	

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Died without suffering clinical failure	38	45		
Suffered clinical failure	48	31		

Attachments (see zip file)	Kaplan-Meier curves/anstatus3.png

Statistical analyses

Statistical analysis title	Logrank test (unstratified) (primary analysis)
Comparison groups	Placebo v Rifampicin

Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Logrank

Statistical analysis title	Logrank test (stratified by site) (2ndry analysis)
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Logrank

Statistical analysis title	Cox model (unstratified) (primary analysis)
Statistical analysis description: Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.32

Statistical analysis title	Cox model (stratified by site) (2ndry analysis)
Statistical analysis description: Hazard ratio is for Rifampicin v Placebo.	
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.31

Secondary: Development of rifampicin resistant S. aureus

End point title	Development of rifampicin resistant S. aureus

End point description:

This endpoint is only applicable to the subset of patients with S. aureus susceptible to rifampicin at randomisation (as the underlying hypothesis is that rifampicin may improve outcomes by increasing the rate of early bacterial killing, results of in vitro sensitivity testing were not required before randomisation).

End point type	Secondary

End point timeframe:

Up to 12 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Not developed rifampicin resistant S. aureus	388	368		
Developed rifampicin resistant S. aureus	0	2		

Attachments (see zip file)	Cumulative incidence/anr.png

Statistical analyses

Statistical analysis title	Analysis

Statistical analysis description:

Risk difference is for Rifampicin - Placebo.

Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Fisher exact
Parameter estimate	Risk difference (%)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.3

Secondary: Serious adverse events

End point title	Serious adverse events

End point description:

Safety analyses include all subjects, regardless of whether or not study drug was actually received. Non-fatal events related to S. aureus bacteraemia are not considered SAEs.

End point type	Secondary

End point timeframe:

Up to 12 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Number of subjects with one or more SAE	94	101		

Attachments (see zip file)	Kaplan-Meier curves/ansae.png

Statistical analyses

Statistical analysis title	Time to first serious adverse event
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Logrank

Secondary: Grade 3 and 4 adverse events

End point title	Grade 3 and 4 adverse events

End point description:

Safety analyses include all subjects, regardless of whether or not study drug was actually received. Non-fatal events related to S. aureus bacteraemia are not considered AEs.

End point type	Secondary

End point timeframe:

Up to 12 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Number of subjects with one or more grade 3/4 AE	131	129		

Attachments (see zip file)	Kaplan-Meier curves/anae.png

Statistical analyses

Statistical analysis title	Time to first grade 3 or 4 adverse event
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank

Secondary: Drug-modifying adverse events

End point title	Drug-modifying adverse events

End point description:

Safety analyses include all subjects, regardless of whether or not study drug was actually received.

A drug-modifying adverse event is defined by a stop or other change (e.g. dose) of antibiotic treatment (study drug or other antibiotic) that is due to an adverse event.

Death and discontinuation of active antibiotic therapy for the current infection treated as competing risks.

End point type	Secondary

End point timeframe:

Up to 12 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Number of subjects with one or more event	39	63		

Attachments (see zip file)	Cumulative incidence/and.png

Statistical analyses

Statistical analysis title	Time to first drug-modifying adverse event

Statistical analysis description:

Death and discontinuation of active antibiotic therapy for the current infection treated as competing risks.

Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Subhazard regression

Secondary: CRP

End point title	CRP

End point description:

Mean (standard deviation) estimated using normal interval regression to account for values above limit of quantification in one centre (that is, CRP only reported as >156 mg/L if above this threshold).

End point type	Secondary

End point timeframe:

Assessments were scheduled on days 0, 3, 10 and 14. Means (standard deviations) below are for day 3. Respective values for day 10 are: placebo 56.7 (56.32), rifampicin 70.2 (66.81); day 14 51.4 (49.15), 73.2 (75.60). Numbers with information as per chart.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: milligram(s)/litre				
arithmetic mean (standard deviation)	90.7 (± 73.87)	100.5 (± 82.59)		

Attachments (see zip file)	Mean CRP/ancrp.png

Statistical analyses

Statistical analysis title	CRP
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [1]
Method	Normal generalized linear regression GEE

Notes:

[1] - Change in CRP from baseline was analysed using a normal generalized linear regression model (using GEE) for a global test of difference between treatment groups across days 3, 10, 14 (independent correlation structure).

Secondary: Bilirubin

End point title	Bilirubin

End point description:

End point type	Secondary

End point timeframe:

Assessments were scheduled on days 0, 3 and 10. Means (standard deviations) below are for day 3. Respective values for day 10 are: placebo 6.7 (6.98), rifampicin 11.0 (12.12). Numbers with information as per chart.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	8.1 (± 9.24)	18.1 (± 16.70)		

Attachments (see zip file)	Mean bilirubin/anresults_bil.png

Statistical analyses

Statistical analysis title	Bilirubin
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Generalized linear regression GEE

Notes:

[2] - Change in bilirubin from baseline was analysed using a normal generalized linear regression model (using GEE) for a global test of difference between treatment groups across days 3, 10 (independent correlation structure).

Secondary: ALT

End point title	ALT

End point description:

End point type	Secondary

End point timeframe:

Assessments were scheduled on days 0, 3 and 10. Means (standard deviations) below are for day 3. Respective values for day 10 are: placebo 23.9 (19.85), rifampicin 23.3 (19.41). Numbers with information as per chart.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	43.4 (± 59.51)	38.4 (± 40.27)		

Attachments (see zip file)	Mean ALT/anresults_alt.png

Statistical analyses

Statistical analysis title	ALT
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [3]
Method	Normal generalized linear regression GEE

Notes:

[3] - Change in ALT from baseline was analysed using a normal generalized linear regression model (using GEE) for a global test of difference between treatment groups across days 3, 10 (independent correlation structure).

Secondary: ALP

End point title	ALP

End point description:

End point type	Secondary

End point timeframe:

Assessments were scheduled on days 0, 3 and 10. Means (standard deviations) below are for day 3. Respective values for day 10 are: placebo 140.8 (108.60), rifampicin 144.9 (98.51). Numbers with information as per chart.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: international unit(s)/litre				
arithmetic mean (standard deviation)	166.9 (± 254.95)	154.0 (± 136.57)		

Attachments (see zip file)	Mean ALP/anresults_alp.png

Statistical analyses

Statistical analysis title	ALP
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [4]
Method	Normal generalized linear regression GEE

Notes:

[4] - Change in ALP from baseline was analysed using a normal generalized linear regression model (using GEE) for a global test of difference between treatment groups across days 3, 10 (independent correlation structure).

Secondary: Duration of bacteraemia

End point title	Duration of bacteraemia

End point description:

End point type	Secondary

End point timeframe:

Only applicable to the subset of patients with repeated blood cultures following randomisation. Numbers below are for day 3. Respective values for day 7 are: placebo 245 not bacteraemic, 1 bacteraemic; rifampicin 211 not bacteraemic, 3 bacteraemic.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
Not bacteraemic	254	243		
Bacteraemic	12	7		

Attachments (see zip file)	Proportions bacteraemic over time/anmicro_bacteraemia.png

Statistical analyses

Statistical analysis title	Duration of bacteraemia
Comparison groups	Placebo v Rifampicin

Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66 [5]
Method	GEE with logistic link

Notes:

[5] - The proportion of patients who were bacteraemic over time was analysed using generalized estimating equations (GEE) with a logistic link for a global test of difference between treatment groups over time (independent correlation structure).

Secondary: Interactions between other medications and study drug

End point title	Interactions between other medications and study drug

End point description:

End point type	Secondary

End point timeframe:

Up to 2 weeks from randomisation.

End point values	Placebo	Rifampicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	370		
Units: Subjects				
No	366	325		
Yes	6	24		
Not recorded	16	21		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Placebo v Rifampicin
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 weeks from randomisation.

Adverse event reporting additional description:

Safety analyses include all subjects, regardless of whether or not study drug was actually received. Non-fatal events related to S. aureus bacteraemia are not considered AEs/SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Rifampicin

Reporting group description: -

Serious adverse events	Placebo	Rifampicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 388 (24.23%)	101 / 370 (27.30%)	
number of deaths (all causes)	56	56	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (inc cysts and polyps)			
subjects affected / exposed	7 / 388 (1.80%)	11 / 370 (2.97%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 5	0 / 8	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	2 / 388 (0.52%)	4 / 370 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			

subjects affected / exposed	12 / 388 (3.09%)	11 / 370 (2.97%)	
occurrences causally related to treatment / all	0 / 12	2 / 11	
deaths causally related to treatment / all	0 / 3	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	12 / 388 (3.09%)	6 / 370 (1.62%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	2 / 388 (0.52%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	0 / 388 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisining and procedural complications			
subjects affected / exposed	5 / 388 (1.29%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders			
subjects affected / exposed	1 / 388 (0.26%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	13 / 388 (3.35%)	5 / 370 (1.35%)	
occurrences causally related to treatment / all	0 / 15	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 6	

Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	5 / 388 (1.29%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 388 (0.26%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	7 / 388 (1.80%)	10 / 370 (2.70%)	
occurrences causally related to treatment / all	0 / 7	2 / 12	
deaths causally related to treatment / all	0 / 2	0 / 5	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 388 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 388 (0.26%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	4 / 388 (1.03%)	10 / 370 (2.70%)	
occurrences causally related to treatment / all	0 / 4	3 / 10	
deaths causally related to treatment / all	0 / 3	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	39 / 388 (10.05%)	37 / 370 (10.00%)	
occurrences causally related to treatment / all	2 / 40	0 / 38	
deaths causally related to treatment / all	0 / 34	0 / 33	

Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	1 / 388 (0.26%)	3 / 370 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Rifampicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 388 (14.95%)	66 / 370 (17.84%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	2 / 388 (0.52%)	1 / 370 (0.27%)	
occurrences (all)	2	1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	5 / 388 (1.29%)	2 / 370 (0.54%)	
occurrences (all)	5	2	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	0 / 388 (0.00%)	1 / 370 (0.27%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	1 / 388 (0.26%)	4 / 370 (1.08%)	
occurrences (all)	1	4	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 388 (0.00%)	1 / 370 (0.27%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			

subjects affected / exposed	5 / 388 (1.29%)	5 / 370 (1.35%)	
occurrences (all)	5	5	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 388 (0.77%)	4 / 370 (1.08%)	
occurrences (all)	3	5	
Investigations			
Investigations			
subjects affected / exposed	6 / 388 (1.55%)	11 / 370 (2.97%)	
occurrences (all)	6	15	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	2 / 388 (0.52%)	4 / 370 (1.08%)	
occurrences (all)	2	4	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	2 / 388 (0.52%)	2 / 370 (0.54%)	
occurrences (all)	2	2	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	6 / 388 (1.55%)	3 / 370 (0.81%)	
occurrences (all)	8	3	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 388 (0.52%)	4 / 370 (1.08%)	
occurrences (all)	2	4	
Eye disorders			
Eye disorders			
subjects affected / exposed	1 / 388 (0.26%)	0 / 370 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	17 / 388 (4.38%)	23 / 370 (6.22%)	
occurrences (all)	20	30	
Hepatobiliary disorders			

Hepatobiliary disorders subjects affected / exposed occurrences (all)	0 / 388 (0.00%) 0	3 / 370 (0.81%) 3	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	6 / 388 (1.55%) 6	4 / 370 (1.08%) 4	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	5 / 388 (1.29%) 5	7 / 370 (1.89%) 7	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 388 (0.52%) 2	0 / 370 (0.00%) 0	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	12 / 388 (3.09%) 12	8 / 370 (2.16%) 8	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	3 / 388 (0.77%) 3	1 / 370 (0.27%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	(i) Remove King's College London (KCL) as Co-Sponsor, and (ii) Add four new trial sites.
14 August 2014	Addition of substudy – Experiences of being approached for trial participation, the consenting process and trial participation.
01 October 2015	Sample size reduced and co-primary endpoint (all cause mortality up to 14 days) reassigned as a secondary endpoint at the request of the funder

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23249501

http://www.ncbi.nlm.nih.gov/pubmed/29249276