Clinical trial results:
A double blind randomised control trial to measure the effect of the addition of clindamycin to flucloxacillin for the treatment of limb cellulitis

Summary

EudraCT number	2013-001218-14
Trial protocol	GB
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	ME/2012/4078

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01876628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Trust Headquarters, Marlborough Street, Bristol, United Kingdom, BS1 3NW
Public contact	Jessica Bisset, University Hospitals Bristol NHS Foundation Trust, 44 117 342 0233, research@UHBristol.nhs.uk
Scientific contact	Jessica Bisset, University Hospitals Bristol NHS Foundation Trust, 44 117 342 0233, research@UHBristol.nhs.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	04 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to see whether the addition of Clindamycin, a protein inhibiting antibiotic, to the standard antibiotic treatment of limb cellulitis, with Flucloxacillin, results in less tissue damage and a more rapid resolution of both systemic and local features, in a cost-effective manner.

Protection of trial subjects:

It is very unusual for people to have any side-effects from the low dose of active capsules which were given to patients, as long as they are careful to follow the instructions about how to take them. Very occasionally however, some people may get slight digestive discomfort or some looseness of stools. Patients were provided with a telephone contact number to ring if they had any worries.

Background therapy:

All patients will be on flucloxacillin. Patients must be in the trial within 48 hours of first dose of flucloxacillin. The flucloxacillin can be either oral (500mg every 6 hours) or intravenous (IV) (1g every 6 hours) but an IV to PO switch should occur as soon as clinically stable.

Evidence for comparator:

The comparator in the trial is a placebo. A comparator was used in order to be able to determine whether the addition of Clindamycin, a protein inhibiting antibiotic, to the standard antibiotic treatment of limb cellulitis, with Flucloxacillin, results in less tissue damage and a more rapid resolution of both systemic and local features, in a cost-effective manner.

Actual start date of recruitment	02 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 410
Worldwide total number of subjects	410
EEA total number of subjects	410

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)	332
From 65 to 84 years	64
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Potential participants were screened from emergency departments, hospital inpatients and referrals to hospital from general practice (family physicians) across 20 hospitals in England.

Pre-assignment

Screening details:

All adult patients with unilateral limb cellulitis were eligible; the key exclusion criteria were antibiotic treatment for longer than 48 hours, previous Clostridium difficile infection, past MRSA carriage, allergy to either penicillin or clindamycin (self-reported or from their medical records), pre-existing diarrhoea and obvious abscess.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Clindamycin Arm

Arm description:

Flucloxacillin, at a minimum of 500mg four times per day for five days, with clindamycin 300mg four times per day for two days given orally

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

Dosage and administration details:

300 mg, four times per day, two days (2.4 g)

Arm title	Placebo

Arm description:

Flucloxacillin, at a minimum of 500mg four times per day for five days, with placebo

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

Dosage and administration details:

300 mg four times per day for two days given orally

Number of subjects in period 1	Clindamycin Arm	Placebo
Started	203	207
Day 5 Follow-Up	160	176
Day 10 Follow-Up	135	151
Completed	123	130
Not completed	80	77
Lost to follow-up	80	77

Baseline characteristics

Reporting groups	
Reporting group title	Clindamycin Arm
Reporting group description:	
Flucloxacillin, at a minimum of 500mg four times per day for five days, with clindamycin 300mg four times per day for two days given orally	
Reporting group title	Placebo
Reporting group description:	
Flucloxacillin, at a minimum of 500mg four times per day for five days, with placebo	

Reporting group values	Clindamycin Arm	Placebo	Total
Number of subjects	203	207	410
Age categorical			
Units: Subjects			
Adults (18-64 years)	166	166	332
From 65-84 years	29	35	64
85 years and over	8	6	14
Age continuous			
Units: years			
arithmetic mean	47.7	50.5	
standard deviation	± 18.4	± 16.9	-
Gender categorical			
Units: Subjects			
Female	74	58	132
Male	129	149	278

End points

End points reporting groups

Reporting group title	Clindamycin Arm
Reporting group description:	
Flucloxacillin, at a minimum of 500mg four times per day for five days, with clindamycin 300mg four times per day for two days given orally	
Reporting group title	Placebo
Reporting group description:	
Flucloxacillin, at a minimum of 500mg four times per day for five days, with placebo	

Primary: Improvement at Day 5 Visit

End point title	Improvement at Day 5 Visit
End point description:	
The primary outcome was improvement at the Day 5 follow-up visit. This was defined in the protocol, as being afebrile (<37.5°C) and either having a reduction in limb swelling (measured by limb circumference) or a reduction in erythema (measured by skin-surface temperature) of 0.2 standard deviations or more for both local measurements. The reduction in limb swelling and limb temperature was determined using the difference between affected and unaffected limbs to reduce confounding by ambient temperature, clothing and posture.	
End point type	Primary
End point timeframe:	
Primary Outcome is measured at Day 5.	

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	172		
Units: Number				
Improved	136	140		
Not Improved	20	32		

Statistical analyses

Statistical analysis title	Primary Outcome Analysis
Comparison groups	Clindamycin Arm v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	3.01

Secondary: Pain Score at Day 10

End point title	Pain Score at Day 10

End point description:

End point type	Secondary

End point timeframe:

10 days

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	151		
Units: Visual Analogue Scale				
median (inter-quartile range (Q1-Q3))	0 (0 to 3)	1 (0 to 3)		

Statistical analyses

Statistical analysis title	Comparison of Day 10 Pain Scores between groups
Comparison groups	Placebo v Clindamycin Arm
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Wilcoxon (Mann-Whitney)

Secondary: Return to normal activities at Day 30

End point title	Return to normal activities at Day 30

End point description:

End point type	Secondary

End point timeframe:

Day 30

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	129		
Units: Number	99	104		

Statistical analyses

Statistical analysis title	Return to normal activities at day 30 by group
Comparison groups	Clindamycin Arm v Placebo
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.774
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.84

Notes:

[1] - This analysis adjusts for the following baseline characteristics due to some observed baseline imbalances between the arms; total affected area, difference between affected and unaffected limb circumferences, difference between affected and unaffected limb temperature and neutrophil count (logged).

Secondary: C-Reactive Protein at Day 10

End point title	C-Reactive Protein at Day 10

End point description:

End point type	Secondary

End point timeframe:

Day 10.

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	148		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	4.95 (2.9 to 15.1)	6 (4 to 11)		

Statistical analyses

Statistical analysis title	C-Reactive Protein at Day 10 between groups
Comparison groups	Clindamycin Arm v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.199
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.66

Notes:

[2] - As C-Reactive Protein follows a log normal distribution the analysis uses the logged value. This means the parameter estimates are ratios of geometric means.
The analysis adjusts for the following baseline characteristics as imbalances between the arms at baseline were observed; total affected area, difference between affected and unaffected limb circumference, difference between affected and unaffected limb temperature, neutrophil count (logged) and the baseline C-Reactive Protein (logged).

Secondary: Urea at Day 5

End point title	Urea at Day 5
End point description:	
End point type	Secondary
End point timeframe:	
Day 5	

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	171		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	4.8 (3.7 to 5.9)	5 (3.9 to 6.1)		

Statistical analyses

Statistical analysis title	Comparison of Urea at Day 5 between groups
Comparison groups	Clindamycin Arm v Placebo
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.085
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.01

Notes:

[3] - As urea follows a log normal distribution, the logarithm has been used in the analysis. This means the parameter estimates are in terms of the geometric means.
The analysis adjusts for the following baseline characteristics as imbalances were observed between the groups; total affected area, difference between the affected and unaffected limb circumference, difference between the affected and unaffected limb temperature, neutrophil (logged) and urea (logged).

Secondary: Neutrophil at Day 5

End point title	Neutrophil at Day 5
End point description:	
End point type	Secondary
End point timeframe:	
Day 5	

End point values	Clindamycin Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	169		
Units: X1000000000/L				
median (inter-quartile range (Q1-Q3))	4.24 (3.12 to 5.7)	4.43 (3.52 to 5.5)		

Statistical analyses

Statistical analysis title	Neutrophil at Day 5 between groups
Comparison groups	Clindamycin Arm v Placebo
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.947
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.09

Notes:

[4] - As the neutrophil count follows a log normal distribution, the logarithm was used in the analysis, so the parameter estimates are in terms of ratios of geometric means.
The analysis adjusts for some baseline characteristics as imbalances were observed between arms; total affected area, difference between unaffected and affected limb circumference, difference between

unaffected and affected limb temperature and neutrophil count (logged).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected at day 5 and day 10. However the total number of serious adverse events reported between day 0 and day 10 have not been broken down by time period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Clindamycin Arm

Reporting group description:

Flucloxacillin, at a minimum of 500mg four times per day for five days, with clindamycin 300mg four times per day for two days given orally

Reporting group title	Placebo

Reporting group description:

Placebo given with Flucloxacillin, at a minimum of 500mg four times per day for five days given alone

Serious adverse events	Clindamycin Arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 203 (3.94%)	15 / 207 (7.25%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 203 (0.00%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Syncope			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 203 (0.00%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
sepsis			
subjects affected / exposed	3 / 203 (1.48%)	8 / 207 (3.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	2 / 203 (0.99%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Clindamycin Arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 203 (27.09%)	40 / 207 (19.32%)	
General disorders and administration site conditions			
Dizziness up to day 5			
subjects affected / exposed[1]	0 / 160 (0.00%)	1 / 176 (0.57%)	
occurrences (all)	0	1	
Dizziness between day 5 and 10			
subjects affected / exposed[2]	0 / 135 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Diarrhoea upto day 5			
subjects affected / exposed[3]	34 / 160 (21.25%)	16 / 176 (9.09%)	
occurrences (all)	34	16	
Diarrhoea between day 5 and day 10			
subjects affected / exposed[4]	17 / 135 (12.59%)	8 / 151 (5.30%)	
occurrences (all)	17	8	
Nausea and vomiting to day 5			
subjects affected / exposed[5]	7 / 160 (4.38%)	3 / 176 (1.70%)	
occurrences (all)	7	3	
Skin and subcutaneous tissue disorders			
Rash upto day 5			
subjects affected / exposed[6]	3 / 176 (1.70%)	8 / 160 (5.00%)	
occurrences (all)	3	8	
Rash between day 5 and day 10			
subjects affected / exposed[7]	2 / 135 (1.48%)	10 / 151 (6.62%)	
occurrences (all)	2	10	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subject exposed to this adverse event is less because fewer patients completed days 0 – 5 and days 5 – 10 days follow up – see section Subject Disposition, table titled 'Number of subjects in period 1'

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported