Clinical trial results:
A prospective single blind randomised controlled study to compare the outcomes of patients with diabetes and clinically non-infected ischaemic and neuropathic foot ulcers treated with and without oral antibiotics - KADFUT

Summary

EudraCT number	2010-022518-16
Trial protocol	GB
Global end of trial date	15 January 2014

Results information

Result version number	v1 (current)
This version publication date	27 August 2020
First version publication date	27 August 2020

Trial information

Trial identification

Sponsor protocol code	KADFUT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Diabetic Foot Clinic, King's College Hospital , +44 020 3299 3223, mbates2@nhs.net
Scientific contact	Diabetic Foot Clinic, King's College Hospital , +44 020 3299 3223, mbates2@nhs.net

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	13 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2014
Global end of trial reached?	Yes
Global end of trial date	15 January 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to investigate whether antibiotics in the treatment of clinically clean neuropathic and ischaemic ulcers in diabetic foot patients could reduce the incidence of infection and therefore lead to improved outcomes .

Protection of trial subjects:

Patients are free to withdraw consent for study treatment and/or consent to participate in the study at any time and without the prejudice to further treatment. Patients who withdraw from study treatment, but are willing to continue to participate in the follow-up visits, should be followed according to the procedures outlined in the protocol.

Patients who develop clinical signs and symptoms of infection in their target or other foot ulcer will be withdrawn. At withdrawal data will be collected as described in the 'early termination visit' and patients followed up 14 days later as per the 'post treatment evaluation'.
Patients who develop drug related adverse events such as gastro intestinal side effects including diarrhoea and vomiting that continue for more than 72 hrs and prevent them from taking antibiotics will also be withdrawn from the study. Patients who develop previously unknown allergies to antibiotics will be withdrawn from the study.

Background therapy:

Standard of care treatment for diabetic foot ulceration without clinical signs of infection. It is generally recommended that patients with ulcers but no purulence should not be treated with antibiotics

Evidence for comparator: -

Actual start date of recruitment	30 April 2012
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited over a period of 21 months at KCH.
First Patient first visit (FPFV) 30/04/2012.
Between January 2012 to October 2012 no recruitment took place.
The trial was terminated before the recruitment target was reached due to slow recruitment, lack of personnel and resources and recruitment had not taken place since 2013.

Pre-assignment

Screening details:

Patients with type 1 or 2 diabetes mellitus, who presented to the Diabetic Foot Clinic at KCH with clean neuropathic or ischaemic diabetic foot ulcers without clinical signs of infection. Patients were recruited over a period of 21 months. Including patients referred from GP surgeries, Primary Care Trusts and other hospitals.

Pre-assignment period milestones

Number of subjects started	17[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen fail: 1

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: The pre-assignment period includes 1 screen fail who was not enrolled into the study

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Blinding implementation details:

Both patients and the Chief Investigator will know the treatment group, however there will be a blinded research team for assessments. Patients will be advised that there will always be two teams of health care professionals monitoring them: the blinded team and the unblinded team .The patient will be asked not to inform the blinded team as to which group they belong.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active group

Arm description:

antibiotics + standard care
The IMPs are licensed antibiotics.
Amoxycillin 500mg /250mg capsules
Flucloxacillin 500mg/250mg capsules
Ciprofloxacin 500mg/250mg tablets
Metronidazole 400mg/200mg tablets
Clarithromycin 500mg/250mg tablets
The above antibiotics will be used for the initial treatment of the patient in the antibiotic group. On follow up visits, patients may continue with their initial antibiotics as prescribed or antibiotics may be adjusted according to the microbiology results of the ulcer culture and microbial sensitivity/resistance (see below). These results are reviewed weekly and antibiotics are changed if necessary.
Doxycycline 100mg capsules
Trimethoprim 200mg/100mg tablets
Sodium fusidate 250mg tablets
Rifampicin 300mg capsules

Co-amoxiclav 625mg/375mg tablets
Co-trimoxazole 480mg
Clindamycin 150mg capsules
Linezolid 600mg tablets
Ceftriaxone sodium 1Gm
Ceftazidime pentahydrate 1Gm
Teicoplanin 400mg/200mg

Arm type	Experimental
Investigational medicinal product name	amoxicillin trihydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 1.5 g per day for up to 20 weeks	
Investigational medicinal product name	flucloxacillin sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 2g per day for up to 20 weeks	
Investigational medicinal product name	metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1.2g per day for up to 20 weeks	
Investigational medicinal product name	ciprofloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1g per day for up to 20 weeks	
Investigational medicinal product name	doxycycline hyclate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 100mg per day for up to 19 weeks	
Investigational medicinal product name	trimethoprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400mg per day for up to 19 weeks	
Investigational medicinal product name	sodium fusidate
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1.5g per day for up to 19 weeks	
Investigational medicinal product name	rifampicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 1200 per day for up to 19 weeks	
Investigational medicinal product name	co-amoxiclav
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1.875g per day for up to 19 weeks	
Investigational medicinal product name	clindamycin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 1.2g per day for up to 19 weeks	
Investigational medicinal product name	clarithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1g per day for up to 20 weeks	
Investigational medicinal product name	ceftriaxone sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: 1g dissolved in 3.5 ml 1% lignocaine for up to 2 weeks	
Investigational medicinal product name	linezolid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1.2g per day for up to 4 weeks	
Investigational medicinal product name	ceftazidime pentahydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:	
3g dissolved in 3.0 ml 1% lignocaine per day for up to 2 weeks	
Investigational medicinal product name	teicoplanin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
400mg dissolved in 3.0mls sterile water per day for up to 2 weeks	
Investigational medicinal product name	co trimoxazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1.920g per day for up to 19 weeks	
Arm title	Control group
Arm description:	
Received standard care for clinically non-infected ischaemic and neuropathic foot ulcers	
Arm type	standard of care
No investigational medicinal product assigned in this arm	

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: There was a blinded research team who performed assessments. The patient and investigator were unblinded.

Number of subjects in period 1	Active group	Control group
Started	7	9
Completed	3	5
Not completed	4	4
Adverse event, non-fatal	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Active group
Reporting group description:	
antibiotics + standard care The IMPs are licensed antibiotics. Amoxycillin 500mg /250mg capsules Flucloxacillin 500mg/250mg capsules Ciprofloxacin 500mg/250mg tablets Metronidazole 400mg/200mg tablets Clarithromycin 500mg/250mg tablets The above antibiotics will be used for the initial treatment of the patient in the antibiotic group. On follow up visits, patients may continue with their initial antibiotics as prescribed or antibiotics may be adjusted according to the microbiology results of the ulcer culture and microbial sensitivity/resistance (see below). These results are reviewed weekly and antibiotics are changed if necessary. Doxycycline 100mg capsules Trimethoprim 200mg/100mg tablets Sodium fusidate 250mg tablets Rifampicin 300mg capsules Co-amoxiclav 625mg/375mg tablets Co-trimoxazole 480mg Clindamycin 150mg capsules Linezolid 600mg tablets Ceftriaxone sodium 1Gm Ceftazidime pentahydrate 1Gm Teicoplanin 400mg/200mg	
Reporting group title	Control group
Reporting group description:	
Received standard care for clinically non-infected ischaemic and neuropathic foot ulcers	

Reporting group values	Active group	Control group	Total
Number of subjects	7	9	16
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			
arithmetic mean	57	65.4	
standard deviation	± 7.1	± 10.6	-
Gender categorical Units: Subjects			
Female	1	0	1
Male	6	9	15

Type of diabetes Units: Subjects			
Type 1 DM	1	0	1
Type 2 DM	6	9	15
Neuropathic: neuroischaemic Units: Subjects			
Neuropathic	6	9	15
Neuroischaemic	1	0	1
Target ulcer Units: Subjects			
Right Foot	3	3	6
Left Foot	4	6	10
Duration of diabetes Units: Years			
arithmetic mean	14	13.7	
standard deviation	± 4.6	± 8.7	-
Ulcer area at presentation Units: cm2			
arithmetic mean	1.2	2.1	
standard deviation	± 1.1	± 2.4	-

End points

End points reporting groups

Reporting group title	Active group
Reporting group description:	
antibiotics + standard care The IMPs are licensed antibiotics. Amoxycillin 500mg /250mg capsules Flucloxacillin 500mg/250mg capsules Ciprofloxacin 500mg/250mg tablets Metronidazole 400mg/200mg tablets Clarithromycin 500mg/250mg tablets The above antibiotics will be used for the initial treatment of the patient in the antibiotic group. On follow up visits, patients may continue with their initial antibiotics as prescribed or antibiotics may be adjusted according to the microbiology results of the ulcer culture and microbial sensitivity/resistance (see below). These results are reviewed weekly and antibiotics are changed if necessary. Doxycycline 100mg capsules Trimethoprim 200mg/100mg tablets Sodium fusidate 250mg tablets Rifampicin 300mg capsules Co-amoxiclav 625mg/375mg tablets Co-trimoxazole 480mg Clindamycin 150mg capsules Linezolid 600mg tablets Ceftriaxone sodium 1Gm Ceftazidime pentahydrate 1Gm Teicoplanin 400mg/200mg	

Reporting group title	Control group
Reporting group description:	
Received standard care for clinically non-infected ischaemic and neuropathic foot ulcers	

Primary: Healing at week 20

End point title	Healing at week 20[1]
End point description:	
patients in each group that are healed at 20 weeks. Healing will be defined as complete epithelialisation which should be present on 2 consecutive weeks.	
End point type	Primary
End point timeframe:	
week 20	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In view of the low numbers of subjects recruited , Analysis of Efficacy Variables was not carried out

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Subjects				
Healed	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to healing of foot ulceration

End point title	Time to healing of foot ulceration

End point description:

End point type	Secondary

End point timeframe:

Baseline to 20 weeks

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: Weeks				
arithmetic mean (standard deviation)				
Healed	8.7 (± 6.5)	6.8 (± 3.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: develop clinical signs of foot infection

End point title	develop clinical signs of foot infection

End point description:

End point type	Secondary

End point timeframe:

Baseline to 20 weeks

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Subjects				
Developed clinical signs of foot infection	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospital admissions related to the foot ulcer

End point title	Number of hospital admissions related to the foot ulcer

End point description:

End point type	Secondary

End point timeframe:

Baseline to 20 weeks

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Subjects				
Admitted to hospital	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of amputations

End point title	Number of amputations

End point description:

End point type	Secondary

End point timeframe:

Baseline to 20 weeks

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Subjects				
Amputations	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse effects of antibiotic treatment

End point title	Adverse effects of antibiotic treatment

End point description:

End point type	Secondary

End point timeframe:
Baseline to 20 weeks

End point values	Active group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Subjects				
Adverse event related to antibiotic treatment	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to week 20	
Adverse event reporting additional description:	
Adverse events will be noted and assessed at weekly visits by the unblinded team	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	32

Reporting groups	
Reporting group title	Active group
Reporting group description:	
antibiotics + standard care The IMPs are licensed antibiotics. Amoxycillin 500mg /250mg capsules Flucloxacillin 500mg/250mg capsules Ciprofloxacin 500mg/250mg tablets Metronidazole 400mg/200mg tablets Clarithromycin 500mg/250mg tablets The above antibiotics will be used for the initial treatment of the patient in the antibiotic group. On follow up visits, patients may continue with their initial antibiotics as prescribed or antibiotics may be adjusted according to the microbiology results of the ulcer culture and microbial sensitivity/resistance (see below). These results are reviewed weekly and antibiotics are changed if necessary. Doxycycline 100mg capsules Trimethoprim 200mg/100mg tablets Sodium fusidate 250mg tablets Rifampicin 300mg capsules Co-amoxiclav 625mg/375mg tablets Co-trimoxazole 480mg Clindamycin 150mg capsules Linezolid 600mg tablets Ceftriaxone sodium 1Gm Ceftazidime pentahydrate 1Gm Teicoplanin 400mg/200mg	
Reporting group title	Control group
Reporting group description:	
Received standard care for clinically non-infected ischaemic and neuropathic foot ulcers	

Serious adverse events	Active group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
acute renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (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			
infected foot ulcer			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences causally related to treatment / all	0 / 0	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	Active group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 9 (77.78%)	
Nervous system disorders			
Vertigo			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haemorrhage			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

dry cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
toe bruising			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
pain in hip			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
foot infection			
subjects affected / exposed	2 / 7 (28.57%)	3 / 9 (33.33%)	
occurrences (all)	2	0	
Cold/flu			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2011	Protocol updated as follows: Inclusion Criteria: Contraception updated to ensure only contraception that is not affected by enzyme inducing antibacterials such as rifampicin is used. Alternatively a barrier method may be added to the original contraceptive method has been added. Exclusion Criteria: Patients who are allergic to Penicillin can be randomised into the trial. Duration of trial updated. Clarifications and administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As it was only possible to recruit 17 patients to this study, it is not possible to reach a conclusion regarding the outcomes of patients with diabetes& clinically non-infected ischaemic&neuropathic foot ulcers treated with & without oral antibiotics

Notes: