



## Clinical trial results:

### Studies of the effects of a one week course of either azithromycin or metronidazole on plasma concentration of procalcitonin in patients with heart failure and elevated plasma procalcitonin concentrations

#### Summary

EudraCT number	2011-004745-40
Trial protocol	GB
Global end of trial date	30 July 2014

#### Results information

Result version number	v1 (current)
This version publication date	22 June 2019
First version publication date	22 June 2019
Summary attachment (see zip file)	Results presentation (Prognostic significance of plasma concentrations of procalcitonin (.pptx)

#### Trial information

##### Trial identification

Sponsor protocol code	n/a
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Hull and East Yorkshire Hospitals NHS Trust
Sponsor organisation address	Anlaby Road, Hull, United Kingdom, HU3 2JZ
Public contact	Prof Andrew Clark, University of Hull, 01482 461775, a.l.clark@hull.ac.uk
Scientific contact	Prof Andrew Clark, University of Hull, 01482 461775, a.l.clark@hull.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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 July 2014
Is this the analysis of the primary completion data?	No
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Global end of trial reached?	Yes
Global end of trial date	30 July 2014
Was the trial ended prematurely?	Yes

Notes:

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## General information about the trial

Main objective of the trial:

In patients with heart failure who have an elevated concentration of procalcitonin (a marker of infection) which is not explained by clinical evidence of infection, can treatment for one week with azithromycin or with metronidazole reduce plasma concentrations of procalcitonin compared to a control group who receive no antibiotics. Procalcitonin is associated with a poor prognosis so understanding the mechanism for an elevated concentration in those without infection may provide a therapeutic target.

Protection of trial subjects:

Patients may stop treatment or withdraw from follow-up at any time without giving a reason. Patients who stop treatment will be asked to have follow-up visits as scheduled. Reasons for withdrawal will be recorded.

Patients will be assessed at the end of a one week course of treatment and one and six weeks after completion. The primary endpoint is the change in plasma concentration of procalcitonin. Side effects will be recorded. This will include laboratory safety data including electrolytes, renal and liver function tests and a 12-lead ECG.

The most likely adverse events are due to gastro-intestinal side effects from antibiotics and those related to the underlying HF problem rather than study medication. Patients with HF are at risk of recurrent hospitalisation for a range of cardiovascular events. Adverse events will be recorded at each visit and all serious adverse events will be reported. Patients will stop medication if the adverse event is attributed to medication and be treated appropriately. All patients will be followed-up for six weeks.

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Background therapy:

None

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Evidence for comparator:

Metronidazole and ciprofloxacin are two medications (vs standard care) in this study are licensed in the UK although not for the treatment of heart failure. We will use generic medication as prescribed to other patients under the hospitals care. Illustrative Summary of Product Characteristics are available at the websites provided below.

Ciprofloxacin (250mg tablets) is indicated for a wide range of respiratory, soft-tissue, gastro-intestinal and chlamydial infections.

Metronidazole (200mg tablets) is an anti-microbial drug with high activity against anaerobic bacteria and protozoa and is indicated for the treatment of such infections including helicobacter pylori and dental infections.

The aim of this pilot study is to determine, in patients with HF and an elevated plasma PCT, whether a one-week course of either ciprofloxacin or metronidazole reduces elevated plasma concentration of PCT compared to a similar observation period without antibiotic treatment. The study is un-blinded but the research scientists performing the PCT assay will be blind to treatment. If antibiotics reduce PCT this suggests that PCT should be used as a potential marker of therapeutic benefit with antibiotic therapy and provides the basis for larger, clinically definitive studies. Alternatively, if PCT does not fall with antibiotic therapy this suggests that elevated PCT reflects patho

Actual start date of recruitment	01 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

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#### Subjects enrolled per age group

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	33
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients will be enrolled from patients observational studies of HF to which patients have already consented to provide a blood sample for research purposes, specifically (REC references): SICA-HF (10/H1313/64), BIOSTAT-HF 11/H1304/5 or HeartCycle/LifeLab (03/02/044).

### Pre-assignment

Screening details:

Blood samples as described in the recruitment section will be analysed for procalcitonin levels. Patients with elevated levels (>50pg/ml) will be approached for participation in the study.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

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

Arm description:

ciprofloxacin 250mg once daily for one week

Arm type	Experimental
Investigational medicinal product name	ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Auricular use

Dosage and administration details:

250mg per day. oral.

<b>Arm title</b>	metronidazole
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Arm description:

200mg three times per day for one week

Arm type	Experimental
Investigational medicinal product name	metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Auricular use

Dosage and administration details:

200mg three times per day for one week

<b>Arm title</b>	Control arm
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Arm description:

no antibiotic treatment

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	ciprofloxacin	metronidazole	Control arm
Started	14	13	13
Completed	14	13	13

## Baseline characteristics

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### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	7	
From 65-84 years	29	29	
85 years and over	4	4	
Age continuous			
Units: years			
median	72		
inter-quartile range (Q1-Q3)	64 to 78	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	27	27	

## End points

### End points reporting groups

Reporting group title	ciprofloxacin
Reporting group description:	ciprofloxacin 250mg once daily for one week
Reporting group title	metronidazole
Reporting group description:	200mg three times per day for one week
Reporting group title	Control arm
Reporting group description:	no antibiotic treatment

### Primary: The primary endpoint is change in PCT from baseline to the evaluation at 7-days in patients who either receive an antibiotic compared to those that do not.

End point title	The primary endpoint is change in PCT from baseline to the evaluation at 7-days in patients who either receive an antibiotic compared to those that do not.
End point description:	
End point type	Primary
End point timeframe:	7 days

End point values	ciprofloxacin	metronidazole	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	13	13	
Units: pg/ml				
number (not applicable)	14	13	13	

### Statistical analyses

Statistical analysis title	Pilot study
Statistical analysis description:	This is a pilot study and as such there is no statistical justification for recruitment size. We seek to measure any reduction in PCT levels in order to inform a larger trial. We will analyse the data using multivariate Cox regression.
Comparison groups	metronidazole v ciprofloxacin

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 7 days post dose.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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### Reporting groups

Reporting group title	Control arm
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Reporting group description: -

Reporting group title	Ciprofoxacin arm
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Reporting group description: -

Reporting group title	Metronidazole
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Reporting group description: -

Serious adverse events	Control arm	Ciprofoxacin arm	Metronidazole
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	1 / 13 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiomyopathy	Additional description: Worsening heart failure		
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation	Additional description: Required hospitalisation		
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

<b>Non-serious adverse events</b>	Control arm	Ciprofoxacin arm	Metronidazole
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 13 (0.00%)
Social circumstances			
Late developer	Additional description: Not true, but inflexibility of the database did not allow non-occurrence of non-serious event to be reported!		
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2012	Submitted to REC
11 September 2012	Submitted to REC

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported