Clinical trial results:
CHANGE TO:
A PILOT RANDOMISED STUDY TO COMPARE COMBINATION ANTIBIOTIC THERAPY (CIPROFLOXACIN AND DOXYCYCLINE) WITH STANDARD THERAPY (BUDESONIDE) IN THE TREATMENT OF ACTIVE CROHN'S DISEASE

Summary

EudraCT number	2008-001137-99
Trial protocol	GB
Global end of trial date	30 May 2019

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020
Summary attachment (see zip file)	End of Study Report (APRICOT End of Study Report.docx)

Trial information

Trial identification

Sponsor protocol code	3591

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01783106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Brownlow Street, Liverpool, United Kingdom,
Public contact	Alex Astor, University of Liverpool, 0151 794 8373, sponsor@liverpool.ac.uk
Scientific contact	Alex Astor, University of Liverpool, 0151 794 8373, sponsor@liverpool.ac.uk
Sponsor organisation name	Royal Liverpool & Broadgreen University Hospitals
Sponsor organisation address	Prescot Street, Liverpool, United Kingdom,
Public contact	Heather Rogers, The Royal Liverpool & Broadgreen University Hospital NHS Trust, 0151 706 3702, Heather.Rogers@lhpspark.nhs.uk
Scientific contact	Heather Rogers, The Royal Liverpool & Broadgreen University Hospital NHS Trust, 0151 706 3702, Heather.Rogers@lhpspark.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	27 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2019
Global end of trial reached?	Yes
Global end of trial date	30 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Primary Objective
•To compare the efficacy of a combination of antibiotics (Ciprofloxacin and Doxycycline) with standard therapy (oral Budesonide - Entocort CR) in the Treatment of Active Crohn’s Disease.

Protection of trial subjects:

As well as the ongoing pharmacovigilance on this study, interim analysis was performed every 6 months to measure tolerability and efficacy. The design of the study, in respect to the frequency of the assessments and interventions, was done with input from patient and public involvement to ensure as little burden as possible was placed on subjects for their compliance with study protocol.

Background therapy:

There was no set baseline medication per se, however patients who were receiving standard of care medication were required to maintain a stable dosage of it for their participation in the study. Prednisolone and Budesonide, as well as Azathioprine or marcaptopurine, were part of the inclusion factors providing the patients could maintain stable dose, the latter two drugs also being strafication factors in patients who had them administered prior to randomisation.

Evidence for comparator:

The Comparison of the combination antibiotics with standard therapy for treating Active Crohn's Disease, taken from protocol:
hydroxychloroquine enhances killing of intra-macrophage bacteria in other conditions and is used, as hydroxychloroquine 200mgs tds in combination with Doxycycline for up to 4 years as first-line therapy in Q-Fever. Our own data, has established in vitro efficacy of Hydroxychloroquine in combination with Doxyclycline and Ciprofloxacin in killing E. coli isolates within macrophages at a steady-state blood concentration of hydroxychloroquine 1-2 micrograms per ml. achievable with hydroxychloroquine 200mg tds dosing in an average adult. This study will be used to assess the efficacy and tolerability of six months' treatment of active Crohn's disease with antibiotics (Ciproflaxin, doxycycline and hydroxychloroquine) selected on the basis of their ability to kill Crrohns' disease E. coli isolates that have been internalised within macrophages in comparison with standard 3 months therapy with the low-side effect steroid, budesonide.

Actual start date of recruitment	25 November 2013
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: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	52
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Sixty one patients were recruited across 8 sites in the United Kingdom. The first patient was recruited on 25 Nov 2013 and the last patient 05 Dec 2018

Pre-assignment

Screening details:

83 patients were screened for the Apricot study, 61 of whom where randomised as they met the inclusion criteria. 17 patients did not meet the inclusion criteria, 4 declined to be a part of the trial and one patient was excluded for other reasons. Out of these 61 patients only 59 went on to receive the study drug.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label study with crossover once randomised, so no blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Experiment arm

Arm description:

4 weeks Combination Antibiotic Therapy (Oral Ciprofloxacin 500mg bd plus Doxycycline 100mg bd and Hydroxychloroquine 200mg tds) followed by a further 20 weeks continued therapy with Doxycycline 100mg bd and Hydroxychloroquine 200mg tds

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	Ciloxan, Cipro, Neofloxin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg twice daily for 4 weeks. Tablets that can be swallowed with water and food

Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	Doryx, Doxyhexal, Doxylin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100mg twice daily for 4 weeks

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg three time daily for 4 weeks

Arm title	Control arm

Arm description:	
The Control group who received the standard of care regimen for study disease	
Arm type	Active comparator
Investigational medicinal product name	Budesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

9mg once daily for 8 weeks, then,
6mg once daily for 2 weeks, then,
3mg once daily for 2 weeks

Number of subjects in period 1[1]	Experiment arm	Control arm
Started	28	33
Completed	20	28
Not completed	8	5
Consent withdrawn by subject	-	1
Transferred to other arm/group	7	-
Did not receive allocated intervention	1	1
Lost to follow-up	-	3

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Crossover into and out of arms was done based on efficacy and not balance, there will therefore be a difference in these numbers

Period 2

Period 2 title	Cross-over
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label study with crossover once randomised, so no blinding

Arms

Are arms mutually exclusive?	No
Arm title	Experiment arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	Ciloxan, Cipro, Neofloxin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg twice daily for 4 weeks. Tablets that can be swallowed with water and food

Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	Doryx, Doxyhexal, Doxylin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
100mg twice daily for 4 weeks

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
200mg three time daily for 4 weeks

Arm title	Control arm

Arm description: -

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

Dosage and administration details:
9mg once daily for 8 weeks, then,
6mg once daily for 2 weeks, then,
3mg once daily for 2 weeks

Number of subjects in period 2	Experiment arm	Control arm
Started	39	39
Completed	39	39

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
Adults (18-64 years)	61	61	
Gender categorical Units: Subjects			
Female	25	25	
Male	36	36	

End points

End points reporting groups

Reporting group title	Experiment arm
Reporting group description:	
4 weeks Combination Antibiotic Therapy (Oral Ciprofloxacin 500mg bd plus Doxycycline 100mg bd and Hydroxychloroquine 200mg tds) followed by a further 20 weeks continued therapy with Doxycycline 100mg bd and Hydroxychloroquine 200mg tds	
Reporting group title	Control arm
Reporting group description:	
The Control group who received the standard of care regimen for study disease	
Reporting group title	Experiment arm
Reporting group description: -	
Reporting group title	Control arm
Reporting group description: -	

Primary: Remission, defined as Crohn's disease activity index (CDAI) less than or equal to 150 at 10 weeks without addition of any other medication or treatment for their Crohn's disease

End point title	Remission, defined as Crohn's disease activity index (CDAI) less than or equal to 150 at 10 weeks without addition of any other medication or treatment for their Crohn's disease
End point description:	
End point type	Primary
End point timeframe:	
CDAI value of less than or equal to 150 at 10 weeks of intervention	

End point values	Experiment arm	Control arm	Experiment arm	Control arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	32	39	39
Units: Number of patients	2	8	7	10

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Experiment arm v Control arm
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Fisher exact
Parameter estimate	Proportions

Primary: Remission, Defined as CDAI of less than or equal to 150 maintained through to 24 weeks

End point title	Remission, Defined as CDAI of less than or equal to 150 maintained through to 24 weeks

End point description:

End point type	Primary

End point timeframe:

CDAI less than or equal to 150 maintained after 24 weeks of intervention

End point values	Experiment arm	Control arm	Experiment arm	Control arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	32	39	39
Units: Number of Patients	2	1	6	1

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Experiment arm v Control arm
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Primary: Remission, defined as CDAI of less than or equal to 150 maintained through to 52 weeks

End point title	Remission, defined as CDAI of less than or equal to 150 maintained through to 52 weeks

End point description:

End point type	Primary

End point timeframe:

Number of patients maintaining remission through to 52 weeks

End point values	Experiment arm	Control arm	Experiment arm	Control arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	32	39	39
Units: Number of patients	1	1	3	1

Statistical analyses

Statistical analysis title	Primary Ednpoint
Comparison groups	Experiment arm v Control arm
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Secondary: Remission and/or Response, defined as a fall in CDAI of more than 70 points at 10 weeks

End point title	Remission and/or Response, defined as a fall in CDAI of more than 70 points at 10 weeks

End point description:

End point type	Secondary

End point timeframe:

Response: Number of patients in whom the CDAI falls by greater than 70 points at 4 week and 10 weeks of intervention, Remission defined as less than or equal to CDAI of 150

End point values	Experiment arm	Control arm	Experiment arm	Control arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	32	39	39
Units: Number of patients	9	11	15	13

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Experiment arm v Control arm

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.01
Method	Fisher exact

Secondary: Remission, Defined as CDAI of less than or equal to 150 at 4 weeks

End point title	Remission, Defined as CDAI of less than or equal to 150 at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

CDAI less than or equal to 150 maintained at 4 weeks of intervention

End point values	Experiment arm	Control arm	Experiment arm	Control arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	32	39	39
Units: Number of patients	4	8	8	9

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Experiment arm v Control arm
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.01
Method	Fisher exact

Secondary: Patient global assessment of symptom severity by visual analogue score

End point title	Patient global assessment of symptom severity by visual analogue score

End point description:

The summaries reported refer to VAS median and IQR at baseline. See Supplementary Figure 3 on the End of Study Report for summaries across all time points.

End point type	Secondary

End point timeframe:

Value of VAS reported by patients at Baseline, 4 weeks, 10 weeks, 24 weeks, 52 weeks

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Scale 1-10				
median (inter-quartile range (Q1-Q3))	3.3 (2.1 to 4.9)	4.1 (2.2 to 5.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fall in Faecal Calprotectin

End point title	Fall in Faecal Calprotectin

End point description:

The summaries reported refer to faecal calprotein median and IQR at baseline. See Supplementary Figure 5 on the End of Study Report for summaries across all time points.

End point type	Secondary

End point timeframe:

Faecal Calprotein levels at baseline and week 10.

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: ug/g				
median (inter-quartile range (Q1-Q3))	497 (265 to 726)	574 (307 to 924)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events and possible drug-related side effects - Nausea

End point title	Adverse Events and possible drug-related side effects - Nausea

End point description:

End point type	Secondary

End point timeframe:

Adverse Events and possible drug-related side effects were assessed at each visit.

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Number of events	24	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events and possible drug-related side effects - Diarrhoea

End point title	Adverse Events and possible drug-related side effects - Diarrhoea

End point description:

End point type	Secondary

End point timeframe:

Adverse Events and possible drug-related side effects were assessed at each visit.

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Number of patients	9	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events and possible drug-related side effects - Mood disturbance

End point title	Adverse Events and possible drug-related side effects - Mood disturbance

End point description:

End point type	Secondary

End point timeframe:

Adverse Events and possible drug-related side effects were assessed at each visit.

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Number of events	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events and possible drug-related side effects - Sleep disturbance

End point title	Adverse Events and possible drug-related side effects - Sleep disturbance

End point description:

End point type	Secondary

End point timeframe:

Adverse Events and possible drug-related side effects were assessed at each visit.

End point values	Experiment arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Number of events	8	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the patient commenced the study drug, until end of study (week 52 or early withdrawal)

Adverse event reporting additional description:

AEs were identified during patients clinic visits with specific questioning as appropriate

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Experiment arm

Reporting group description:

4 weeks Combination Antibiotic Therapy (Oral Ciprofloxacin 500mg bd plus Doxycycline 100mg bd and Hydroxychloroquine 200mg tds) followed by a further 20 weeks continued therapy with Doxycycline 100mg bd and Hydroxychloroquine 200mg tds

Reporting group title	Control

Reporting group description:

The Control group who received the standard of care regimen for study disease

Serious adverse events	Experiment arm	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 39 (12.82%)	1 / 39 (2.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Intestinal obstruction	Additional description: Small bowel obstruction for conservative management (CRP262). Follow up with surgical operation		
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease	Additional description: Worsening of patient's underlying Crohn's disease to warrant discontinuation of the study intervention.		
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abcess			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis	Additional description: Rhabdomyolsis secondary to fall Sepsis? source		
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (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	Experiment arm	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)	30 / 39 (76.92%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Poor peripheral circulation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)	2 / 39 (5.13%)	
occurrences (all)	2	2	

Pyrexia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Swelling			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Respiratory symptom			
subjects affected / exposed	3 / 39 (7.69%)	6 / 39 (15.38%)	
occurrences (all)	3	8	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Mood altered			
subjects affected / exposed	4 / 39 (10.26%)	6 / 39 (15.38%)	
occurrences (all)	4	7	
Sleep disorder			
subjects affected / exposed	8 / 39 (20.51%)	9 / 39 (23.08%)	
occurrences (all)	8	10	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Incisional hernia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Sunburn			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiovascular symptom			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	5 / 39 (12.82%)	5 / 39 (12.82%)	
occurrences (all)	5	5	
Hypoaesthesia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

Migraine			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Taste disorder			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Asthenopia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	4 / 39 (10.26%)	2 / 39 (5.13%)	
occurrences (all)	6	2	
Abdominal pain upper			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Anal incontinence			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Anal ulcer			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Anorectal discomfort			

subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Defaecation urgency			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	9 / 39 (23.08%)	6 / 39 (15.38%)	
occurrences (all)	9	7	
Dry mouth			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 39 (12.82%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
Glossodynia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Haematemesis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Mouth ulceration			

subjects affected / exposed	1 / 39 (2.56%)	5 / 39 (12.82%)	
occurrences (all)	1	6	
Nausea			
subjects affected / exposed	19 / 39 (48.72%)	7 / 39 (17.95%)	
occurrences (all)	24	7	
Proctalgia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Rectal tenesmus			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Blister			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Hair disorder			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

Night sweats			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Photosensitivity reaction			
subjects affected / exposed	7 / 39 (17.95%)	1 / 39 (2.56%)	
occurrences (all)	7	1	
Pruritus			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Dysuria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 39 (12.82%)	1 / 39 (2.56%)	
occurrences (all)	5	1	
Back pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Rhabdomyolysis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Tendon pain			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Anal candidiasis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	
occurrences (all)	2	0	

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	0 / 39 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 December 2008	An Amended Protocol/Substantial amendment was required by MHRA so that clinical trial authorisation could be obtained on trial. Amended protocol should be submitted to address the following: - As patients might be elderly and/or have been on corticosteroid therapy, exclusion criteria should include a history of tendon disorders related to fluroquinolone administration in accordance with the SmPC
02 April 2009	An Amended Protocol/Substantial amendment is required to make some essential changes to clarify trial procedures, making changes where necessary to ensure trial is not bias, trial data is credible, patients safety maintained by adding Data Monitoring committee and finally to correct a number of administration errors. Amended protocol should be submitted to address the following: - Addition of Data Monitoring Committee - Addition of Study Team - Change in Secondary End-point Endoscopy changed from 12 weeks to 10 weeks - Change from Single Blind to open label trial
31 March 2010	NO PATIENTS WERE RECRUITED WITH THE GIVEN PROTOCOL, MAINLY DUE TO THE NEED TO STOP AZATHIOPRINE TO ALLOW TRIMETHOPRIM TREATMENT, THERE WAS ALSO RELUCTANCE TO TAKE METRONIDAZOLE FOR 3 MONTHS. FOLLOWING ADVICE FROM AN INDEPENDENT DATA MONITORING COMMITTEE AND THE TRUST GOVERNANCE ADVISOR (PROFESSOR TOM WALLEY) WE DECIDED TO CHANGE THE ANTIBIOTIC COMBINATION TO CIPROFLOXACIN AND DOXYCYCLINE A COMBINATION THAT HAS BEEN USED LONG TERM FOR OTHER INDICATIONS AND THAT IS EQUALLY SUPPORTED (COMPARED WITH CIPROFLOXACIN, TRIMETHOPRIM, METRONIDAZOLE) BY IN VITRO DATA OF EFFICACY AGAINST E. COLI IN MACROPHAGES (THAT TARGET ORGANSIMS IN THIS TRIAL). 1. CHANGE IN ANTIBIOTIC FROM CIPROFLOXACIN, METRONIDAZOLE AND TRIMETHOPRIM TO CIPROFLOXACIN AND DOXYCYCLINE 2. FOR ALL PATIENTS ENTERING THE STUDY, 1 ADDITIONAL BLOOD SAMPLE WILL BE TAKEN, THE SERUM WILL BE STORED AND USED FOR E-COLI ANTIBODY TESTING IN THE UNITED STATES OF AMERICA. INFORMATION HAS BEEN ADDED IN PROTOCOL, PATIENT INFORMATION SHEET AND CONSENT FORM 3. ADDITION OF STUDY TEAM MEMBERS
06 December 2011	Addition of hydroxychloroquine. Update of the primary endpoint - To compare the efficacy of a combination of antibiotics (ciproflaxin and doxycicline together with hydroxychloroquine) with standard therapy (oral budesonide) in the treatment of active crohn's disease. Update to primary outcome measures. Change of medication schedule, with an additional 20 weeks of continued therapy of Doxyclcine and Hydroxychloroquine. Option of patients who are randomised to Budenoside to cross over after lack of favourable response. added exclusion criteria related to hydroxychloroquine tolerance.
04 January 2013	Update of protocol to exclude patients who are receiving methotrexate due to concerns over the safety in interactions with this drug and Ciprofloxacin and Doxycycline.

01 August 2013	Added extra biopsies to the protocol for faecal calprotectin. Adoption of study by LCTU and so update to the Pharmacovigilance section in line with their systems/SOPs. Change to consent form to confirm patients are happy with copy being sent to the RLBUHT (new co-sponsor)
04 April 2014	change of CI - Professor Chris Probert took over from Prof. Probert Update of inclusion criteria related to acceptable levels of C reactive protein in patients entering the study. Changes to the sites running the study.
03 August 2016	Addition of new sites to the study. Change of appendix to specify tricylcic antidepressants that are not permitted (previous just stated "trycyclic antidepressants"). addition of windows before or after schedule assessment to allow for scheduling issues at sites. update on definition of source documentation in the light of recent changes in local practices to reduce physical/paper records.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported