Clinical trial results:
A Phase II trial of broad spectrum antibiotic therapy for early stage chronic lymphocytic leukaemia.

Summary

EudraCT number	2010-022260-12
Trial protocol	GB
Global end of trial date	21 March 2016

Results information

Result version number	v1 (current)
This version publication date	31 October 2018
First version publication date	31 October 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (CLEAR Clinical Trial Report.pdf)

Trial information

Trial identification

Sponsor protocol code	1947

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01279252
WHO universal trial number (UTN)	-
Other trial identifiers	REC Number: 10/H0715/75

Notes:

Sponsors

Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Professor Stephen Devereux, King's College Hospital, 0044 2032999000, stephen.devereux@kcl.ac.uk
Scientific contact	Professor Stephen Devereux, King's College Hospital, 0044 2032999000, stephen.devereux@kcl.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	01 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2016
Global end of trial reached?	Yes
Global end of trial date	21 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether patients with previously untreated, early stage chronic lymphocytic leukaemia (CLL) respond to empirical broad spectrum antibiotics and therefore test the hypothesis that occult bacterial infection is responsible for the induction and maintenance of CLL.

Protection of trial subjects:

The study will be stopped if more than 27 patients (15% of 180) experience grade 3-4 severe adverse reactions

Background therapy:

none

Evidence for comparator:

n/a

Actual start date of recruitment	05 July 2011
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: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	80
From 65 to 84 years	16

85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 8 NHS clinical sites in the United Kingdom between 2011 and 2016.

Pre-assignment

Screening details:

Previously untreated patients with monoclonal B lymphocytosis and stage A CLL

Period 1

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

Blinding implementation details:

N,A

Arms

Arm title	Single Arm

Arm description:

Single arm phase II study in previously untreated patients with monoclonal B lymphocytosis and stage A CLL

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

Dosage and administration details:

400mg orally twice each day for 14 days.

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

Dosage and administration details:

Clarithromycin 500mg orally twice per day for 14 days

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

Dosage and administration details:

Ciprofloxacin 500mg orally twice per day for 14 days

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

Dosage and administration details:

Lansoprazole 30mg orally twice per day for 14 days.

Number of subjects in period 1	Single Arm
Started	98
Completed	88
Not completed	10
Adverse event, non-fatal	10

Baseline characteristics

End points

End points reporting groups

Reporting group title	Single Arm

Reporting group description:

Single arm phase II study in previously untreated patients with monoclonal B lymphocytosis and stage A CLL

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

Overall response rate [Complete Remission (CR) + Partial Remission (PR)] at 6 months.

End point type	Primary

End point timeframe:

First dose to 6months

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: See attached document for results. Primary endpoint was not met.

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: whole	88			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of CTCAE grade 2 or above treatment related toxicity from day 1 to 6 weeks.

End point title	Incidence of CTCAE grade 2 or above treatment related toxicity from day 1 to 6 weeks.

End point description:

Incidence of CTCAE grade 2 or above treatment related toxicity from day 1 to 6 weeks.

End point type	Secondary

End point timeframe:

Until 6 weeks post dose.

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: whole	88			

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow minimal Residual Disease (MRD) status in patients who achieve CR at 6 months.

End point title	Bone marrow minimal Residual Disease (MRD) status in patients who achieve CR at 6 months.

End point description:

Bone marrow minimal Residual Disease (MRD) status in patients who achieve CR at 6 months.

End point type	Secondary

End point timeframe:

Baseline to 6 months post dose

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: whole	88			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate [Complete Remission (CR) + Partial Remission (PR)]

End point title	Overall response rate [Complete Remission (CR) + Partial Remission (PR)]

End point description:

Overall response rate [Complete Remission (CR) + Partial Remission (PR)] at 12 months based on clinical and peripheral blood measurements.

End point type	Secondary

End point timeframe:

Baseline to 12 months post dose

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: whole	88			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline until 30 days post completion of antibiotic treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Whole Trial
Reporting group description:	
All participants in single arm trial.	

Serious adverse events	Whole Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 98 (3.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Transischaemic event			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Palpitations and shortness of breath			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
hallucinations, bad dreams and change in mood.			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Whole Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 98 (71.43%)		
Nervous system disorders			
neurological			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	6		
General disorders and administration site conditions			
Lethargy			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	8		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	60 / 98 (61.22%)		
occurrences (all)	60		
Nausea & vomiting			
subjects affected / exposed	40 / 98 (40.82%)		
occurrences (all)	40		
Dysguesia			
subjects affected / exposed	17 / 98 (17.35%)		
occurrences (all)	17		
generic GI			
subjects affected / exposed	14 / 98 (14.29%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
skin issues			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Psychiatric disorders			

Psychological subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5		
Infections and infestations infection subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2012	Protocol changed to allow sites a choice of proton pump inhibitor as not all sites stock Lansoprazole. Protocol changed to include secondary endpoint of response rate at 12 months. An extra visit has been added as patients may achieve remission after 6 months. 12 month evaluation visit added
21 December 2012	Addition of three subgroups of participants:- 1. Monoclonal B lymphocytosis (MBL) with a raised lymphocyte count and CLL phenotype. This condition is considered to be a precursor of CLL and is associated with a 1% per year risk of developing disease requiring therapy. 2. Good risk Binet stage A CLL with fewer than two poor prognostic markers and an absence of adverse cytogenetics. 3. Poor risk Binet stage A CLL with 2 or more adverse prognostic markers.
14 November 2013	Expansion of Primary Endpoint to - "Overall response rate [Complete Remission (CR) + Partial Remission (PR)] at 6 months as defined by the International Workshop on CLL and the National Cancer Institute"
25 June 2014	Clarification of IMP and permitted concomitant medication:- All patients will receive a 14 day course of the following agents: Metronidazole 400mg tablets. One to be taken po twice a day. Clarithromycin 500mg tablets. One to be taken po twice a day. Ciprofloxacin 500mg tablets. One to be taken po twice a day. Lansoprazole 30mg tablets. One to be taken po twice a day orOmeprazole 20mg tablets/capsules. One to be taken po twice a day

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.

The primary endpoint was not met.

Notes: