Clinical Trial Summary Report

Date of Report:

May 30th 2017

Protocol title:

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

CLEAR: CLL empirical antibiotic regimen

Protocol number:

EudraCT Number	2010-022260-12
REC Number	10/H0715/75
IRAS project ID:	59948

Study Centre(s):

Kings College Hospital, London
Princes Royal University Hospital Farnborough
St James University Hospital, Leeds
Royal Liverpool Hospital
Royal Bournemouth Hospital
Royal Free Hospital LondonUniversity Hospital of Wales, Cardiff
The Christie Hospital, Manchester

Study Initiation and Final Completion Dates:

Study initiation: 27th June 2011

Study completion: 21st March 2016

Phase of Development:

Phase 2

Study Objectives:

Primary Objective

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.

Study design.

Multi-centre, open label, single arm phase II study in previously untreated patients with monoclonal B lymphocytosis and stage A CLL

Schedule of Activities.

Parameter	Screening Visit	Baseline / Day 1 Visit	Day 7 Interim Safety Check (via telephone)	6 Week Safety Visit	6 Month Evaluation Visit	12 Month Evaluation Visit
Visit window		**Minimum 4 weeks from screening**	**+/- 2 days**	**30 days after finishing antibiotic regimen +/- 2 days**	**6 months from starting antibiotics +/- 7 days**	**12 months from starting antibiotics +/- 14 days**
Informed consent	X					
Medical History	X	X				
ECOG performance score	X	X				
Physical Examination To include assessment of lymphadenopathy, hepatomegaly, splenomegaly, vital signs [temperature (°C), BP (mm/Hg), pulse rate (bpm)]	X	X		X	X	X
FISH	X1					
IgVH sequencing	X1					
Immunophenotyping	X1				X2	
Haematology bloods	X3	X3		X4	X3	X3
Biochemistry bloods To include: Renal – Creatinine Liver – AST, ALP, GGT, total bilirubin	X	X		X		
Serum or Urine HCG		X5				
Eligibility Checks		X				
Blood Sample for CLL Biobank		X6			X6	
Mouthwash Sample for CLL Biobank		X6				
Treatment Regimen		X7				
Concomitant Treatment	X	X	X	X		
Adverse Events		X8	X8	X8		
Bone marrow aspirate and trephine biopsy To include assessment of morphology and MRD					X9	

1. To be performed if not previously conducted for the RESPECT study (NRES protocol: 09/H1008/122). Tests undertaken at Haematological Malignancy Diagnostic Service, Leeds (HMDS).
2. Tests undertaken at HMDS.
3. To include: white cell count, platelet count, neutrophil count, lymphocyte count and haemoglobin level.
4. To include: white cell count, platelet count, neutrophil count and haemoglobin level.
5. For women of childbearing potential only.
6. CLL Biobank samples (CLL Biobank Liverpool)
7. Antibiotic regimen administered on days 1 to 14
8. Adverse events to be monitored continually from day 1 to 6 week safety visit.
9. To be performed on patients in apparent CR on clinical and peripheral blood criteria. Tests undertaken at HMDS.

Number of Subjects (Planned and Analysed):

Cohort	Planned	Analyzed	Completed Rx
1. Good risk stage A CLL	71	79	70
2. Monoclonal B lymphocytosis	71	13	12
3. Adverse risk stage A CLL	38	6	6

Main Criteria for Inclusion:

Group 1 Good risk stage A CLL

Age $\geq$ 18

ECOG performance status of 2 or less.

Typical CLL as reported by HMDS.

Clinical stage A disease. All of:

- B lymphocyte count >5x10^9/l
- Haemoglobin >10g/dl
- Platelets >100x10^9/l
- Lymphadenopathy = 2 or fewer sites

No disease progression over a minimum of 1 month prior to commencement of therapy. All of:

- lymphocyte doubling time > 12 months
- stable blood counts: <1g/dl fall in haemoglobin, <50x10^9/l fall in platelets
- lymph nodes liver and spleen, <50% increase in size

Less than 2 adverse prognostic factors from:

- CD38 expression >7%
- Unmutated Vh genes (>98% homology with germline)

Absence of adverse cytogenetics

- Deletion of chromosome 11q22 (>20% by FISH)
- Deletion of chromosome 17p13 (>20% by FISH)

Expected survival > 6 months

Able to give informed consent

No clinical evidence of active infection at the time of study entry

No known allergy to any of the study medications

Renal and liver function tests within normal limits

Group 2. Monoclonal B-lymphocytosis (MBL)

Age $\geq$ 18

ECOG performance status of 2 or less.

MBL with typical CLL phenotype

Clinical stage MBL. All of:

- B lymphocyte count >1.5x10^9/l but <5x10^9/l
- Haemoglobin >10g/dl
- Platelets >100x10^9/l

Lymphadenopathy = 2 or fewer sites

No disease progression over a minimum of 1 month prior to commencement of therapy. All of:

- lymphocyte doubling time > 12 months
- stable blood counts: <1g/dl fall in haemoglobin, <50x10^9/l fall in platelets
- lymph nodes liver and spleen, <50% increase in size

Expected survival > 6 months

Able to give informed consent

No clinical evidence of active infection at the time of study entry

No known allergy to any of the study medications

Renal and liver function tests within normal limits

Group 3: Adverse risk stage A CLL

Age $\geq$ 18

ECOG performance status of 2 or less.

Typical CLL as reported by HMDS.

Diagnosis made within 6 months of date of screening[♤]

Clinical stage A disease. All of:

- B lymphocyte count >5x10^9/l
- Haemoglobin >10g/dl
- Platelets >100x10^9/l
- Lymphadenopathy = 2 or fewer sites

No disease progression over a minimum of 1 month prior to commencement of therapy. All of:

- lymphocyte doubling time > 12 months
- stable blood counts: <1g/dl fall in haemoglobin, <50x10^9/l fall in platelets
- lymph nodes liver and spleen, <50% increase in size

2 or more adverse prognostic factors from:

- CD38 expression =/>7%
- Unmutated Vh genes (>98% homology with germline)
- Adverse cytogenetics: either or both of:
  - Deletion of chromosome 11q22 (>20% by FISH)
  - Deletion of chromosome 17p13 (>20% by FISH)

Expected survival > 6 months

Able to give informed consent

No clinical evidence of active infection at the time of study entry

No known allergy to any of the study medications

Renal and liver function tests within normal limits

♤ This criterion will apply once the good risk and MBL cohorts are fully recruited. This should minimise the number of screen failures by reducing the entry of good risk patients.

Study Treatment:

Drug
Metronidazole tablets
Clarithromycin tablets
Ciprofloxacin tablets
Lansoprazole capsules or omeprazole tablets/capsules (according to local site preference of proton pump inhibitor)
Nystatin oral suspension
Domperidone

Efficacy Endpoints:

Primary Endpoint

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

Secondary Endpoints

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

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

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

Subjects Analysed:

	Number of Subjects
Registered (Consented)	148
Received Treatment (Safety)	98
Prematurely Withdrawn	10
Efficacy Evaluable	88

Efficacy Results:

No responses were observed at the 6-month timepoint. The study thus failed to meet it's primary endpoint.

Safety Results:

Patients Prematurely Withdrawn from Study

Subject Number	**Date Started Treatment**	**Date of Withdrawal**	**Reason for Withdrawal**
22	10/04/12	12/04/12	Nausea & vomiting
27	02/05/12	05/05/12	Nausea
37	17/07/12	22/7/12	Sore mouth
45	10/09/12	13/09/12	Diarrhoea
51	08/10/12	15/10/12	Rash
55	04/12/12	08/12/12	Diarrhoea
65	03/01/13	05/01/13	Diarrhoea
78	23/04/13	25/04/13	Vomiting & diarrhoea
85	07/11/13	10/11/13	Diarrhoea
87	06/01/14	08/01/14	Diarrhoea

Adverse Reactions

There were 169 adverse events reported by 70 patients

By grade:

Grade	Number of AEs	Number of patients with this as worst grade
1	133	44
2	28	18
3	3	3
4	0	0
Not graded	6	5
Total	169	70

Adverse events by grade and type

Symptom	Total	Not graded	1	2	3
Diarrhoea	60	4	42	12	2
Nausea/Vomiting	40		36	4	
Dysguesia	17		14	3	
Other GI	14	1	13		
Lethargy	8		7	1	
Other/Unknown	7	1	4	1	1
Neurological	6		5	1	
Infection	6		3	3	
Psychological	5		4	1	
Skin	2		2		
Musculoskeletal	2		2		
Cardiac	1		1		
Cancer	1			1	

SAEs, SARs or SUSARs

No SAEs, SARs or SUSARs were reported

CONCLUSIONS:

Did the study achieve its objectives:

Yes, in part. We successfully evaluated the effect of broad-spectrum antibiotics on early stage good risk chronic lymphocytic leukaemia.

The main findings:

There was no evidence that early stage chronic lymphocytic leukaemia responds to broad spectrum oral antibiotics. About 1 in 8 patients were unable to tolerate a 2-week course of triple antibiotic therapy.

Arrangements for publication or dissemination of research, including any feedback to participants:

The results will be published as a short report in a haematology journal