Clinical trial results:
A phase II trial of Cyclosporin A in Early Adverse Risk CLL

Summary

EudraCT number	2012-002795-13
Trial protocol	GB
Global end of trial date	04 April 2016

Results information

Result version number	v1 (current)
This version publication date	20 April 2017
First version publication date	20 April 2017

Trial information

Trial identification

Sponsor protocol code	RG_12-129

Additional study identifiers

ISRCTN number	ISRCTN61297219
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Cancer Research Clinical Trials Unit, Institute of Cancer and Genomic Sciences, United Kingdom, B15 2TT
Public contact	Yolande Jefferson, University of Birmingham, 0044 1214159179, y.c.jefferson@bham.ac.uk
Scientific contact	Yolande Jefferson, University of Birmingham, 0044 1214159179, y.c.jefferson@bham.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	06 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2014
Global end of trial reached?	Yes
Global end of trial date	04 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of CsA on tumour kinetics in patients with CLL.

Protection of trial subjects:

The study protocol involves more visits to hospital than would usually be required and also extra blood tests than would be performed in standard clinical care.

The risks of these extra tests are minimal and these are routine procedures. It is possible that treatment with Ciclosporin (CsA) may improve patient outcome. All patients will benefit from close monitoring during the trial period.

As with all medications, treatment with Ciclosporin (CsA) has potential side effects of which all trial staff and patients are fully informed.

Background therapy:

The only treatment provided in the study is Ciclosporine (CsA).

Evidence for comparator:

Not available.

Actual start date of recruitment	15 October 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: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	3
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial Open to Recruitment: 29-Apr-2013
First Patient Registered: 05-Aug-2013
Last Patient Last Visit: 03-Nov-2014

Pre-assignment

Screening details:

N/A: No screening assessments involved. Please refer to the protocol for the eligibility criteria.

Period 1

Period 1 title	Early Phase II (Overall period) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Treatment

Arm description:

Patients who commenced Cyclosporin A Treatment

Arm type	Experimental
Investigational medicinal product name	Cyclosporin A
Investigational medicinal product code	
Other name	Ciclosporine; CsA
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Treatment will commence at week 5 of Cycle 1. CsA will be started at a dose of 5mg/kg/day to be taken orally in two divided doses.

Number of subjects in period 1	Treatment
Started	5
Completed	4
Not completed	1
incidental finding of atrial fibrillation	1

Baseline characteristics

Reporting groups	
Reporting group title	Early Phase II (Overall period)
Reporting group description:	
This group contains the full number of patients that took part in the phase II part of the study.	

Reporting group values	Early Phase II (Overall period)	Total	
Number of subjects	5	5	
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			
median	64.8		
inter-quartile range (Q1-Q3)	55.68241 to 72.09309	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	5	5	
Spleen Units: Subjects			
Palpable	0	0	
Not Palpable	5	5	
Not preformed	0	0	
Unknown	0	0	
Liver Units: Subjects			
Palpable	0	0	
Not palpable	5	5	
Not performed	0	0	
Unknown	0	0	
Lymph Nodes Units: Subjects			
Palpable	0	0	
Not palable	5	5	
Not performed	0	0	
Unknown	0	0	

CLL Stage Units: Subjects			
Stage A	5	5	
Stage B	0	0	
ECG status Units: Subjects			
Normal	4	4	
Abnormal	1	1	
Previous CLL Units: Subjects			
Yes	1	1	
No	4	4	
Previous treatment for CLL Units: Subjects			
Yes	1	1	
No	4	4	
Positive cells			
This was done in 4 patients			
Units: 2-40			
median	19		
inter-quartile range (Q1-Q3)	8 to 55.5	-	
Haemoglobin Units: 180			
median	138		
inter-quartile range (Q1-Q3)	134 to 146	-	
Platelets 109/L Units: 200			
median	185		
inter-quartile range (Q1-Q3)	143 to 228	-	
White blood cell Units: 130			
median	44.7		
inter-quartile range (Q1-Q3)	34.8 to 45	-	
Neutrophils Units: 2-40			
median	4.5		
inter-quartile range (Q1-Q3)	4.5 to 4.5	-	
Lymphocytes Units: 10			
median	38.5		
inter-quartile range (Q1-Q3)	29.6 to 41	-	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Patients who commenced Cyclosporin A Treatment	

Primary: Change in proliferation rate of CLL cells after 4 weeks

End point title	Change in proliferation rate of CLL cells after 4 weeks[1]
End point description:	
The number and proportion of patients achieving a positive reduction defined as at least a 50% reduction in proliferation rate after 4 weeks of CsA will be reported as a proportion of the number of patients recruited.	
End point type	Primary
End point timeframe:	
after 4 weeks	

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: No formal statistical analysis was conducted only descriptive analysis were performed

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: 2-40				
Complete Response	0			
Partial Response	0			
Stable Disease	4			
Progressed disease	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change in proliferation rate of CLL cells after 4 weeks

End point title	Change in proliferation rate of CLL cells after 4 weeks[2]
End point description:	
The mean reduction in proliferation rates after 4 weeks of CsA therapy will be reported with 95% confidence interval.	
End point type	Primary
End point timeframe:	
after 4 weeks	

Notes:

[2] - 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: No formal statistical analysis was conducted only descriptive analysis were performed

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: 2-40				
arithmetic mean (confidence interval 95%)	-0.049 (-0.268 to 0.169)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of loss of labelled CLL cells from the circulation with CsA therapy

End point title	Rate of loss of labelled CLL cells from the circulation with CsA therapy

End point description:

Rate of loss of labelled CLL cells from the circulation with CsA therapy

End point type	Secondary

End point timeframe:

Full treatment period (up to 6 months)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: absolute figure				
arithmetic mean (confidence interval 95%)				
Cycle 0	2.02 (-4.42 to 8.46)			
Cycle 1	2.16 (-1.62 to 5.93)			
Cycle 2	0.36 (-0.38 to 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous intra-patient variation in the proliferation, release and loss of CLL cells from the circulation.

End point title	Spontaneous intra-patient variation in the proliferation, release and loss of CLL cells from the circulation.

End point description:

Spontaneous intra-patient variation in the proliferation, release and loss of CLL cells from the circulation.

End point type	Secondary

End point timeframe:

Full treatment period (up to 6 months)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: absolute figure				
arithmetic mean (confidence interval 95%)				
cycle 0	0.491 (-0.02 to 1)			
cycle 1	0.244 (0.08 to 0.4)			
cycle 2	0.254 (-0.01 to 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum release of labelled CLL cells into the circulation with CsA therapy.

End point title	Time to maximum release of labelled CLL cells into the circulation with CsA therapy.

End point description:

Time to maximum release of labelled CLL cells into the circulation with CsA therapy.

End point type	Secondary

End point timeframe:

Full treatment period (up to 6 months)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: days				
arithmetic mean (confidence interval 95%)				
Cycle 0	16.5 (2.17 to 30.82)			
Cycle 1	9.2 (-3.98 to 22.38)			
Cycle 2	7.25 (-0.256 to 14.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity of CsA in patients with CLL (toxicities will be measured and graded according to CTCAE criteria v4)

End point title	Toxicity of CsA in patients with CLL (toxicities will be measured and graded according to CTCAE criteria v4)

End point description:

Toxicity of CsA in patients with CLL (toxicities will be measured and graded according to CTCAE criteria v4)

These are all described cleared in the adverse event breakdown section

End point type	Secondary

End point timeframe:

Full treatment period (up to 6 months)

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: distinct values	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all AEs (as stipulated in the trial protocol) will be documented and reported from the date of registration until 30 days after the administration of the last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Treatment

Reporting group description:

All patients who started the CsA treatment.

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			

Flushing			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	4		
Localised oedema			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	4		
High neutrophils			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
High lymphocytes			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
High WBC			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Atrial fibrillation			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	6		
Memory impairment			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Paresthesia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymph node pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
High MCH			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Low RBC			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Eye disorders			

Flashing lights subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Oral dysethesia subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	4 / 5 (80.00%) 5 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Sensitive hands and feet subjects affected / exposed occurrences (all) Warm palms subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Muscle weakness lower limb subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3 1 / 5 (20.00%) 1		

Back pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Infections and infestations EBV reactivation subjects affected / exposed occurrences (all) ear infection subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1		
Metabolism and nutrition disorders Hypomagnesmia subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2012	Following initial application to the MHRA, a change was requested by the ethics committee to the protocol in order to obtain approval. It was requested that a statement was added so that it was clear that in the event of pregnancy, the patient must stop trial treatment. The protocol was therefore updated to version 2.0 and a change made to the patient information sheet to clarify patients must stop study treatment in the event of pregnancy.
29 July 2013	Cycle 1 now optional- Update to protocol, PIS and GP letter to reflect change Update to exclusion criteria- the following exclusion criteria: Complex cytogenetics: Two or more abnormalities detected by FISH and/or conventional cytogenetics. We initially excluded patients with complex cytogenetics based on the fact that the disease is less likely to be dependent on the microenvironment in this cohort. However, it transpires that the first two patients screened with clinically very stable disease, previously thought to be good candidates for this trial had complex cytogenetics. Therefore, we now believe that we misjudged the affect that this exclusion criterion would have on patient selection, and as it is leading to the exclusion of otherwise suitable candidates we no longer feel that it is an appropriate selection condition. The Patient Information Sheet has been updated to clarify that the first of the three labelling cycles is now optional. More detail has been added to explain which are compulsory parts of the study and which parts are optional. Also, a schema has also been added to help the patient visualise the treatment schedule and understand what the trial will involve for them. In addition, we have clarified the section relating to patient samples. This is to highlight that although no new samples will be taken from a patient if they withdraw from the study, samples previously taken will be retained for future ethically approved projects. Correction of typo to PIS and Consent Form post acceptance
07 May 2014	New day 56 sample- The protocol has been updated to include a further sample at the end of each cycle. In practical terms this means drawing an extra 1ml of blood when the patient attends clinic on Day 0 for cycle 1 and for cycle 2 and an extra 5ml of blood at an extra visit on day 56 of cycle 2. These samples will be used to assess if the patient has any remaining labelled CLL cells circulating in their system. These results will then be used to reset the baseline for each cycle and to obtain a final reading of cell death at the end of the three cycles. A new patient document has been produced, the Release of Medical Information Form. The purpose of this document is to provide a means of obtaining consent for monitoring pregnancies that occur in trial patients or the partners of trial patients. This form is being implemented only as a precaution in case pregnancy does occur, pregnancies are not expected in this trial and when entering the trial patients consent to use two forms of contraception whilst on the trial and for three months after they stop the trial medication to prevent pregnancy occurring.

12 January 2015	The SmPC was previously combined with Neoral Oral Solution. The SmPC for all ciclosporin products has been harmonised throughout Europe. All sections of the SmPC have been updated. As the update has included a change to the Undesirable Effects section, section 7.5 of the Protocol has been updated accordingly. In addition, section 7.3.2 and 7.4.1 have been updated to reflect changes to the sample processing that are required to introduce new sites to the trial. Southampton Hospital were unable to process samples locally so these samples will now be frozen locally and collected in batches before being processed centrally at King's College London. Finally, the trial contact list has been updated to reflect new staff members working on the trial at the CRCTU. PIS and RSI amended to reflect 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.

There was a very small number of subjects recruited, therefore it would be expected that analysis would be primarily surround safety and intra-patient analysis.

Notes: