Clinical trial results:
Phase II Trial of Fludarabine & Cyclophosphamide followed by Thalidomide for Angioimmunoblastic Lymphoma

Summary

EudraCT number	2005-003931-40
Trial protocol	GB
Global end of trial date	08 January 2014

Results information

Result version number	v1 (current)
This version publication date	09 December 2016
First version publication date	09 December 2016

Trial information

Trial identification

Sponsor protocol code	BRD/05/95

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00958854
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Public Contact, CR UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific Contact, CR UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.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	20 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the response rate of patients treated with FluCy (Fludarabine and cyclophosphamide) chemptherapy.

Protection of trial subjects:

FluCy chemotherapy can affect the patients' sperm or egg cells & might harm an unborn child. If there was a chance that a patient or the partner of a patient could become pregnant, they had to agree to use a reliable form of contraception during the trial and for at least 6 months after the last trial treatment. All women of childbearing potential at risk of becoming pregnant had to undergo a pregnancy test at screening or during baseline investigations.

If on day 28 of any cycle of FluCy chemotherapy there was persistent grade 3 to 4 haematological toxicity not related to marrow involvement, treatment could be delayed for up to 2 weeks with a reduction in the doses of Fludarabine and Cyclophosphamide by 25%. Supportive care should have been given as per local practice, but since delayed nausea may occur with this regimen, at least 5 days of antiemetic treatment with a 5-HT3 antagonist was recommended. Patients also received Co-Trimoxazole or Pentamidine prophylaxis for at least six months after the end of FluCy chemotherapy & blood EBV levels were monitored. For the prevention of transfusion related graft-versus-host disease, all cellular blood products administered following treatment with Fludarabine had to be irradiated. FluCy has marked stem cell toxicity and peripheral blood progenitor cells should were harvested early in patients considered candidates for high-dose chemotherapy as second line treatment.
For grade 1 or 2 toxicities such as constipation, fatigue, sedation, skin rash, tremor or oedema, adequate supportive care should have been provided. For any persistent grade 2 toxicity (grade 1 if neuropathy), the dose escalation should have been halted. For grade 3 or 4 toxicity (grade 2 if neuropathy) Thalidomide should have been discontinued. It should have been resumed at half the dose after one week if the toxicity had subsided. Any persistent grade 3 toxicity (grade 2 if neuropathy) should have led to the discontinuation of Thalidomide treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2009
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	5
From 65 to 84 years	9
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients with newly diagnosed AITL presenting to one of the trial sites were screened for eligibility to enter this study.
The participating investigators kept a complete anonymised log of all patients screened for eligibility who were not registered in the trial either because they were ineligible or because they decline participation.

Period 1

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

Arms

Arm title	FluCy & Thalidomide

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for solution for injection/infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

FluCy is was given as a three-day regimen repeated every 28 days. Formal restaging was carried out after four cycles of FluCy. If at that point patients had not experienced at least a partial response FluCy was stopped. At the discretion of the treating physician, responding patients who had not achieved a complete remission after four courses of FluCy could be given a maximum of six courses.

FluCy was given by mouth as standard for this study. However, in patients with marked disease-related gastrointestinal symptoms or in those with poor tolerability of oral FluCy, the intravenous route of administration could be used after discussion with the chief investigator. Oral fludarabine was given at 40mg/m2, and intravenous fludarabine was given at 25mg/m2

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

FluCy is was given as a three-day regimen repeated every 28 days. Formal restaging was carried out after four cycles of FluCy. If at that point patients had not experienced at least a partial response FluCy was stopped. At the discretion of the treating physician, responding patients who had not achieved a complete remission after four courses of FluCy could be given a maximum of six courses.

FluCy was given by mouth as standard for this study. However, in patients with marked disease-related gastrointestinal symptoms or in those with poor tolerability of oral FluCy, the intravenous route of administration could be used after discussion with the chief investigator. Oral cyclophosphamide and intravenous cylophosphamide were given at 250mg/m2

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard

Routes of administration	Oral use

Dosage and administration details:

Patients were on continuous oral Thalidomide four weeks after the beginning of the last cycle of FluCy. Thalidomide 50 mg hard capsules were be prescribed at the initial dose of 100 mg daily. The daily dose was increased by 100 mg every 4 weeks to the maximum of 300 mg. The Thalidomide treatment was to be continued for at least six months, unless disease progression occurred earlier. In responding patients, the continuation of Thalidomide therapy beyond six months was at the discretion of the treating physician.

Number of subjects in period 1	FluCy & Thalidomide
Started	15
Completed	1
Not completed	14
Allergic reaction to Thalidomide	1
Adverse event, non-fatal	2
Not known	1
Death	3
Disease Progression	6
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Inclusion Criteria
• Patients with a new diagnosis of angioimmunoblastic lymphoma and measurable (ie anatomically assessable) disease
• WHO/ECOG performance status of 0, 1 or 2
• Age > 18 years
• Negative pregnancy test if the patient is of childbearing potential
• Prepared to comply with the contraceptive measures stipulated by the Thalidomide Celgene Pregnancy Prevention Programme Signed consent form.

Exclusion Criteria
• Prior chemotherapy for AITL
• Active second malignancy or other concomitant serious medical condition, in particular peripheral neuropathy
• Known seropositivity for HBV, HCV or HIV
• Breast feeding
• Severe impairment of renal or liver function (defined as serum creatinine, bilirubin or alkaline phosphatase > 2.5 times the upper limit of normal).

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5	5	
From 65-84 years	9	9	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	5	5	
Male	10	10	

End points

End points reporting groups

Reporting group title	FluCy & Thalidomide

Reporting group description: -

Primary: Response rate after FluCy chemotherapy

End point title	Response rate after FluCy chemotherapy[1]

End point description:

End point type	Primary

End point timeframe:

Response is assessed following Fludarabine and Cyclophosphamide Chemotherapy

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: As advised on 23/Jun/16 by Chersoni Raffaella from the EMA service desk: we can post the result without entering the details of the statistical analysis because currently the system cannot accommodate one arm study.

End point values	FluCy & Thalidomide			
Subject group type	Reporting group			
Number of subjects analysed	15[2]			
Units: number of patients with complete respons				
Complete Response (CR)	5			
Unconfirmed CR	1			
Partial Response (PR)	3			
Stable Disease (SD)	0			
Progressive Disease (PD)	4			
Not assessable	2			

Notes:

[2] - Two patients only received one cycle of FluCy and response was not assessable in these patients

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and end of trial had to be recorded in the patient notes and the trial CRFs.

Adverse event reporting additional description:

Grade 3 or 4 haematological toxicity occurred in eight (53%) patients, grade 3 or 4 non-haematological toxicity was experienced in nine (60%) patients

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Fludarabine & cyclophosphamide followed by Thalidomide

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AE line listings were not reported in the final publication for this study and are therefore not provided on the results database. Grade 3 or 4 haematological toxicity occurred in eight (53%) patients, grade 3 or 4 non-haematological toxicity was experienced in nine (60%) patients.

Serious adverse events	Fludarabine & cyclophosphamide followed by Thalidomide		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Guillain Barre Syndrome			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Rigors/Chills			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Fever			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage - upper GI NOS			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm, wheezing			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria	Additional description: Urine colour change		

subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infection - Upper respiratory				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with grade 4 neutrophils				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection - Urinary tract infection NOS				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection - normal neutrophils				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection (pneumonia) - lung				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection - Diarrhoea norovirus + campylobactirtive				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection - Lower respiratory tract				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection - normal ANC			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fludarabine & cyclophosphamide followed by Thalidomide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2006	All reference to Thalidomide supplied by Pharmion has been removed from the protocol. The Thalidomide will now be supplied by Durbin PLC who are acting as agents for the importing company Essential Nutrition Ltd. Durbin do not operate a Risk Management Programme for Thalidomide use, so it has been stipulated in the protocol, that in order for sites to particpate in the study, they must provide evidence that their site and NHS Trust have a Risk management Programme and pregnancy testing schedule in place prior to recruiting patients. Failure to provide such evidence will result in the site being suspended from participating in the study any further. The associated trial documentation such as the PIS and GP letter state that the patient must be willing or shall be monitored through the Risk Management mechanisms in place at their treatment site. The Lymphoma Trials Office has also moved location and this information has now been amended on the protocol.
01 December 2007	The Thalidomide for the trial will no longer be supplied through Durbin PLC, instead participating sites will be responsible for supplying all of the IMPs for the trial from their own pharmacy stocks. These drugs are Fludarabine, Cyclophosphamide and Thalidomide. This information has been detailed in the protocol under section 21. Clearer information regarding the diagnostic and research samples to be taken has been provided under section 12. The pharmacovigilance section has also be expanded substantially to ensure that all reporting guidelines required by the Regulatory Authorities are met and that there is a robust Risk management and pregnancy testing schedule in place at each site due to the involvement of thalidomide in this trial. The PIS, Consent form and GP letter have been amended accordingly to reflect the various changes made to the protocol.
20 January 2009	submission of copies of the sample labels to be used in this trial as requested in the CTA notice of acceptance dated 12th April 2006
05 February 2009	Changes have been made to the protocol, Patient information, consent form and GP letter. The change reflects the current availability and licensing of thalidomide in the UK by the supplier, Pharmion. All sites from now on will be supplied this drug by Pharmion. Name of contact in the general information section was changed, more information was given on the responsibility for the conduct of the study. Information in the safety assessment and pharmacovigilance section and expected adverse events was also changed.
15 June 2009	To notify that the Leeds Teaching Hospitals NHS Trust clinical trials website will contain information about this trial. This will be limited to the trial title, inclusion and exclusion criteria and primary endpoints.
21 June 2010	An audit of information about contraception given in Patient Information Sheets (PIS) compared with that given in SmPCs was carried out at our trials centre, and we found that the information in the PIS for this trial was incorrect (ie we told them to use contraception but not for as long as they ought to according to the SmPCs). The PIS was amended with revised guidance regarding contraception

12 April 2011	A list of amendments made to the main protocol, are as follows: The following changes were made to the CT application form: Section A: • Update to the sponsor's protocol code number • Inclusion of the US NCT number Section B: • Update of the sponsor's contact details • Addition of the contact point designated by the sponsor CANCER RESEARCH UK & UCL CANCER TRIALS CENTRE Cancer Research UK & UCL Cancer Trials Centre University College London Haematology Trials Director: Professor J A Ledermann 90 Tottenham Court Road London W1T 4TJ Tel: +44 (0)20 7679 9538 Fax: +44 (0)20 7679 9861 e-mail: aitl@ctc.ucl.ac.uk website: www.ctc.ucl.ac.uk General CTC Enquiries Tel: +44 (0)20 7679 9898 Fax:+44 (0)20 7679 9899 UCL Cancer Ins titute Section C: • Update to the request for Authorisation to Competent Authority Section D: • Update to IMPs information Section E: • Additional Information to the trial information – MedDRA • Change in the definition of 'End of Trial' • Addition of the recruitment start date Section G: • Addition of a central technical facility Section H: • Change of National Competent Authority details
16 May 2011	We are proposing the following changes to the labelling for the IMPs that were submitted as a substantial amendment for this Clinical Trial on 20 January 2009, which was subsequently issued with a notice of acceptance on 06 February 2009: Dispensing labels for Fludarabine, Cyclophosphamide and Thalidomide We would like to retract the dispensing labels for Fludarabine, Cyclophosphamide and Thalidomide that were submitted. Regarding the IV drugs (Fludarabine, Cyclophosphamide and Thalidomide), we propose not to apply IMP labelling to them as we believe their use falls under the remit of Regulation 46(2) of the Medicines for Human Use (Clinical Trials) Regulations, for the following reasons: 1) The IMPs are marketed products, used broadly within their authorisations (i.e. cancer). 2) The IMPs will be dispensed to subjects in accordance with a prescription given by an authorised health care professional 3) The IMPs will be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 that apply in relation to dispensed relevant medicinal products Regarding the oral drugs (Fludarabine, Cyclophosphamide and Thalidomide), abridged labels will be used.
28 June 2011	Sponsor decided to modify the indemnity wording based on comments made by the National Research Ethics Service Committee. Therefore, following amendment was made to protocol version 5.0: • The original wording of the Indemnity section of the protocol, section 22.2, was reinstated.

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.

AE line listings were not reported in the final publication for this study, and are therefore not provided on the results database.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27001186