Clinical trial results:
Phase II study of low intensity allogeneic transplantation in Mantle Cell Lymphoma

Summary

EudraCT number	2007-003081-18
Trial protocol	GB
Global end of trial date	25 July 2019

Results information

Result version number	v1 (current)
This version publication date	26 August 2020
First version publication date	26 August 2020

Trial information

Trial identification

Sponsor protocol code	BRD/07/137

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00720447
WHO universal trial number (UTN)	-
Other trial identifiers	CTA number: 02666/0001/001, Cancer Research UK reference number: C7627/A9080

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom,
Public contact	Public contact, Cancer Research UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, Cancer Research 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	23 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2018
Global end of trial reached?	Yes
Global end of trial date	25 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to document the toxicity, feasibility and survival following reduced intensity allogeneic transplantation
from HLA-compatible sibling or unrelated donors in patients with untreated Mantle Cell Lymphoma. The primary endpoint is progression free survival.

Protection of trial subjects:

Stem-cell transplantations in the trial were conducted at experienced transplant centres familiar with the conditioning regimen. However, the centres may not have used it in this group of patients at this timepoint. The transplant and post-transplant procedures followed standard protocol.

Campath (alemtuzumab) was used outside of its licensed indication (licensed for B-cell chronic lymphocytic leukaemia which is a low-grade NHL, as mantle cell lymphoma is). However, BEAM-Campath regimen has been routinely used as a conditioning regimen in allogeneic transplant to reduce the incidence of Graft Versus Host Disease for low grade lymphomas. Sites were required to keep drug accountability records. Only investigators/nurses experienced in using these IMPs according to the protocol were delegated treatment responsibilities. IDMC met annually to review safety data.

Patients underwent screening evaluations to confirm eligibility for the trial, including full history and physical examination, pregnancy tests, biochemical examinations assessing liver and renal function, β2 microglobulin, serum LDH, virology (HIV, HBV, HCV, CMV and VZV status), assessment of cardiac function, confirmation of tissue type, STR analysis and ABO blood group. Donors were assessed for suitability for transplant, type of donor and CMV status.

Patients were assessed regularly and the protocol gave guidance for supportive care for Graft versus host disease prophylaxis, infection prophylaxis and DLI therapy.

Female patients potentially able to child bear needed to have a negative pregnancy test prior to commencing the trial drugs. Patients or their partners were recommended to use a barrier method of contraception during treatment and for one year after the last trial treatment.

Background therapy:

Not Applicable

Evidence for comparator:

The study is single arm and therefore no comparators were used.

Actual start date of recruitment	06 January 2010
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	22
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited to the trial on 06/01/2010. The final patient was recruited on 10/09/2013. In total, 25 patients were recruited and 12 sites were activated of which 8 recruited to the trial.

Pre-assignment

Screening details:

No screening information to provide for this trial. Patients were screened for eligibility for inclusion into the trial as per trial protocol.

Period 1

Period 1 title	Main trial (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	BEAM-Campath low intensity conditioning regimen

Arm description:

All patients will receive the BEAM-Campath low intensity conditioning regimen outlined below prior to the allogeneic transplant.

BCNU (Carmustine) 300mg/m2 administered over 2 hours on day -6 via IV (if Carmustine supplies are limited, site could administer Lomustine (CCNU) at a dose of 200mg/m2)
Campath (Alemtuzumab): 10mg, administered over 2 hours on days -5 to -1 transplant via IV
Ara-C (Cytarabine): 200mg/m2 two times a day, administered over 15 minutes on days -5 to -2 inclusive via IV
Etoposide: 200mg/m2, administered over >1 hour on days -5 to -2 inclusive via IV
Melphalan: 140mg/m2, adminisitered on day -1 via IV bolus

Donor peripheral stem cell collection and patient administration of stem cells:
G-CSF mobilised Peripheral blood stem cells (PBSC) are preferred (>4x106 CD34 + cells/kg) and should be collected as per local policy. However bone marrow may be used (nucleated cell dose > 3 x 108/kg required). Collection and administration of PBSC as per local policy.

Arm type	Single
Investigational medicinal product name	BCNU
Investigational medicinal product code	
Other name	Carmustine
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

300mg/m2 to be administered via IV over 2 hours on day -6 prior to transplant.

Investigational medicinal product name	Campath
Investigational medicinal product code	
Other name	Alemtuzumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg to be administered via IV over 2 hours on days -5 to -1 inclusive prior to infusion.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C

Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

200mg/m2 of Cytarabine to administered twice a day via IV over 15 minutes on days -5 to -2 inclusive prior to transplant.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide 200mg/m2 to be administered via IV over >1 hour every day from day -5 to day -2 inclusive prior to transplant.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Melphalan 140mg/m2 administered via IV bolus on day -1 prior to transplant.

Investigational medicinal product name	Lomustine
Investigational medicinal product code	
Other name	CCNU
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In the event Carmustine supplies are limited, oral Lomustine (dose 200mg/m2) can be substituted (day -6 prior to transplant).

Number of subjects in period 1	BEAM-Campath low intensity conditioning regimen
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	BEAM-Campath low intensity conditioning regimen

Reporting group description:

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G-CSF mobilised Peripheral blood stem cells (PBSC) are preferred (>4x106 CD34 + cells/kg) and should be collected as per local policy. However bone marrow may be used (nucleated cell dose > 3 x 108/kg required). Collection and administration of PBSC as per local policy.

Reporting group values	BEAM-Campath low intensity conditioning regimen	Total	
Number of subjects	25	25	
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)	22	22	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	3	3	
Male	22	22	
ECOG PS			
ECOG PS at diagnosis			
Units: Subjects			
ECOG score 1	13	13	
ECOG score 0	12	12	
Disease stage at diagnosis Units: Subjects			
Stage 1	1	1	
Stage 3	5	5	
Stage 4	19	19	
Bulky disease			

Units: Subjects			
Absent	18	18	
Present	7	7	
Response to induction chemotherapy Units: Subjects			
CR	11	11	
PR	14	14	
MIPI Units: Subjects			
Low risk	15	15	
Intermediate risk	4	4	
High risk	4	4	
Missing	2	2	
Donor matching Units: Subjects			
Matched sibling	11	11	
MUD	14	14	
Time from diagnosis to AlloSCT Units: Days			
median	274		
full range (min-max)	98 to 485	-	
Age at transplant Units: Years			
median	54		
full range (min-max)	34 to 70	-	

End points

End points reporting groups

Reporting group title	BEAM-Campath low intensity conditioning regimen

Reporting group description:

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G-CSF mobilised Peripheral blood stem cells (PBSC) are preferred (>4x106 CD34 + cells/kg) and should be collected as per local policy. However bone marrow may be used (nucleated cell dose > 3 x 108/kg required). Collection and administration of PBSC as per local policy.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[1]

End point description:

The sample size was calculated using a Fleming design so is based on a number of patients alive and progression free at this point. 15/25 needed. The K-M estimate at 2 years was 68·0% (95% CI: 46·1–82·5), the plot is also given.

End point type	Primary

End point timeframe:

The primary endpoint is the number of patients alive and progression free at 2 years.

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: This was a single arm trial based on a Fleming design. The primary endpoint required 15/25 patients to be alive and progression free at 2 years - this does not require a statistical test. The K-M rate and it's confidence interval have also been presented in the description.

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Patients				
Alive an progression free	17			
Progressed or died before 2 years	8			

Attachments (see zip file)	PFS K-M curve/BJH-2018-01364.R1 - figure 2 a PFS large.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description: K-M rate at 3 years with 95% CI	
End point type	Secondary
End point timeframe: OS at 3-years	

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	80 (58.4 to 91.2)			

Attachments (see zip file)	OS K-M curve/BJH-2018-01364.R1 - figure 2 b OS.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Non-relapse mortality (NRM)	
End point title	Non-relapse mortality (NRM)
End point description: Cumulative incidence of non-relapse mortality at 2 years. This is calculated using competing risks (relapse counted as a competing event)	
End point type	Secondary
End point timeframe: NRM at 2 years	

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	13 (4.4 to 35.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of relapse

End point title	Cumulative incidence of relapse

End point description:

End point type	Secondary

End point timeframe:

Cumulative incidence of relapse at 2 years. This is calculated using competing risks with NRM counting as a competing event.

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	21 (9.3 to 43.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Graft vs Host Disease (GvHD)

End point title	Acute Graft vs Host Disease (GvHD)

End point description:

One patient who failed to engraft was excluded.

End point type	Secondary

End point timeframe:

GvHD which occurs within 100 days of transplant

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	24[2]			
Units: Patients				
Grade I	7			
Grade II	2			
No acute GvHD reported	15			

Notes:

[2] - One patient failed to engraft and was excluded from GvHD analyses.

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic Graft Vs Host disease (GvHD)

End point title	Chronic Graft Vs Host disease (GvHD)

End point description:

End point type	Secondary

End point timeframe:

Chronic GvHD is GvHD occurring after Day 100

End point values	BEAM-Campath low intensity conditioning regimen			
Subject group type	Reporting group			
Number of subjects analysed	24[3]			
Units: Patients				
Limited	6			
Extensive	8			

Notes:

[3] - One patient who failed to engraft was excluded from all GvHD analyses

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occur between informed consent and 30 days post transplant. Note, non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after.

Adverse event reporting additional description:

Advsrse events were recorded on trial CRFs. Serious Adverse Events were reported on SAE Report.
AEs and SAES: Relationships are to treatment (i.e. any IMP)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	BEAM-Campath low intensity conditioning regimen

Reporting group description:

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Serious adverse events	BEAM-Campath low intensity conditioning regimen		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	1		
Investigations			
Laboratory test abnormal	Additional description: Low cyclosporine level		
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Headache				
alternative dictionary used: MedDRA 23				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fever				
alternative dictionary used: MedDRA 23				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chest wall pain				
alternative dictionary used: MedDRA 23				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infection with normal ANC				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Opportunistic infection	Additional description: Opportunistic infection (CMV)			
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphopenia	Additional description: Opportunistic infection lymphopenia			
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with unknown ANC			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	BEAM-Campath low intensity conditioning regimen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)		
Investigations			
Haemoglobin			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[1]	17 / 24 (70.83%)		
occurrences (all)	17		
Neutrophil count			
subjects affected / exposed[2]	24 / 24 (100.00%)		
occurrences (all)	24		
Platelet count			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[3]	8 / 24 (33.33%)		
occurrences (all)	8		
Weight loss			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[4]	9 / 24 (37.50%)		
occurrences (all)	9		
Bilirubin			
subjects affected / exposed[5]	2 / 24 (8.33%)		
occurrences (all)	2		
Calcium deficiency			

subjects affected / exposed[6]	3 / 24 (12.50%)		
occurrences (all)	3		
Phosphate - serum low			
subjects affected / exposed[7]	2 / 24 (8.33%)		
occurrences (all)	2		
Potassium - serum low			
subjects affected / exposed[8]	4 / 24 (16.67%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed[9]	3 / 24 (12.50%)		
occurrences (all)	3		
Headache			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[10]	5 / 24 (20.83%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[11]	14 / 24 (58.33%)		
occurrences (all)	14		
Fever			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[12]	15 / 24 (62.50%)		
occurrences (all)	15		
mucositis			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[13]	20 / 24 (83.33%)		
occurrences (all)	20		
Oedema			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[14]	2 / 24 (8.33%)		
occurrences (all)	2		
Blood and lymphatic system disorders			

Oedema peripheral			
subjects affected / exposed[15]	2 / 24 (8.33%)		
occurrences (all)	2		
Immune system disorders			
Anaphylactic reaction	Additional description: Allergy/ Anaphylaxis		
alternative dictionary used: MedDRA 23			
subjects affected / exposed[16]	4 / 24 (16.67%)		
occurrences (all)	4		
Eye disorders			
Dry eye			
subjects affected / exposed[17]	2 / 24 (8.33%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed[18]	3 / 24 (12.50%)		
occurrences (all)	3		
anorexia			
subjects affected / exposed[19]	13 / 24 (54.17%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed[20]	7 / 24 (29.17%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed[21]	23 / 24 (95.83%)		
occurrences (all)	23		
Heartburn			
subjects affected / exposed[22]	2 / 24 (8.33%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed[23]	22 / 24 (91.67%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed[24]	9 / 24 (37.50%)		
occurrences (all)	9		
Abdominal pain			
alternative dictionary used: MedDRA 23			

subjects affected / exposed[25]	2 / 24 (8.33%)		
occurrences (all)	2		
Proctalgia			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[26]	2 / 24 (8.33%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed[27]	3 / 24 (12.50%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[28]	4 / 24 (16.67%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed[29]	7 / 24 (29.17%)		
occurrences (all)	7		
Rash			
subjects affected / exposed[30]	14 / 24 (58.33%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Back pain			
alternative dictionary used: MedDRA 23			
subjects affected / exposed[31]	4 / 24 (16.67%)		
occurrences (all)	4		
Infections and infestations			
Fungal infection			
subjects affected / exposed[32]	2 / 24 (8.33%)		
occurrences (all)	2		
Neutropenic sepsis			
subjects affected / exposed[33]	10 / 24 (41.67%)		
occurrences (all)	10		
Infection	Additional description: infection with unknown anc		

subjects affected / exposed[34] occurrences (all)	2 / 24 (8.33%) 2		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial

transplant but failed to engraft and had non-trial transplant soon after

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[20] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[21] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[22] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[23] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[26] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[27] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[28] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[29] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[30] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[31] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after
[32] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[33] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

[34] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: non-serious AE data is provided for 24 patients as one trial patient received a trial transplant but failed to engraft and had non-trial transplant soon after

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2009	Pg 3: The name of the Lymphoma Trials Office has been changed to the Haematology Trials Group. A study outline has been provided in section 1.1 Sect 7: The inclusion and exclusion criteria for registration and for proceeding to allograft have been amalgamated into one section to make this clearer for sites. Sect 9: This has been updated in line with the current procedures at the Cancer Trials Centre Sect 10.2: A sentence regarding the substitution of Lomustine for Carmustine has been added. This is due to Carmustine supplied currently being limited in the UK. Sect 11.6: Information regarding Lomustine Drug Supply, Formulation, Administration and Storage has been added. Sect 12.2: A paragraph about supportive care for patients taking part in this regimen has been added. Sect 14: It has been decided to monitor chimerism for 2 years only, not 3 years. This is standard for all transplant patients. Sect 15: Point number 3 has been removed as there is no 8 week scan in this trial. This was incorrect in the previous version. Sect 16: It has been decided to follow patients up every 3 months for 2 years, and then annually until death. This follows the standard follow up procedure for transplant patients.S Sect 16.1.2: Time to engraftment has been added as an investigation at 3 months post transplant, in order to assess the degree of success of the transplant. Sect 18: This section has been updated to reflect the new phamacovigilance template released at the Cancer trials centre. Appendix 1: Glossary, has been moved from the start of the protocol into an Appendix. App 4: Assessment of GvHD, has been added as Appendix 4, as there was previously no assessment information for GvHD contained in the protocol. App5 : Expected AEs. This section includes Expected Adverse Event for all the IMP's concerned in this trial, and has been entered in the updated format as required by the Cancer Trials Centre. App 6: Assessment Schedule: A schedule of Assesments included
29 July 2010	Inclusion criteria has been amended to allow for buccal swab to be taken from patient and donor for chimerism studies prior to transplant in section 7.1 • Exclusion criteria has been amended to clarify the serology positivity for HIV, HBV and HCV in section 7.2 • Exclusion criteria has been amended to clarify what inadequate cardiac function is (ejection fraction must be > 50% if assessed by ECHO or >40% if assessed by radionuclide ventriculography in section 7.2 • Bone marrow aspirates and trephines will be required only at 3 months post transplant if there is a prior involvement in section 16.1.2 • A requirement that patients should begin therapy with the study drug within 2 weeks of registration has been added in section 9.0. • The requirement for sites to do an evaluation of expectedness of SAEs has been removed from section 18.2.2 and transferred to UCL CTC • A requirement to obtain consent to report information from the mother if not a trial patient in case of pregnancy has been added in section 18.5 and a new Pregnancy Partner Information Sheet and Consent Form have been created • A list of AEs expected for the treatment regimen post allogeneic transplant has been added. A reference to the most recent SmPC for each of the IMPs has been included in case when the event does not appear on the list of AEs for the treatment regimen. Previous lists of AEs for each separate IMP have been removed. • The following new sections have been added to the protocol: section 7.3 on informed consent, section 7.4 on screening logs, section 7.6 on pregnancy and birth control, section 12.4 on management after treatment withdrawal, section 20.0 on trial closure and archiving, section 21.0 on trial monitoring and oversight, section 22.0 on data management guide, section 23.0 on withdrawal of patients

27 October 2012	The following changes have been made to the MiniAllo protocol • A section (6.1.2) on training requirements for site staff has been included • A section (8.1.1) clarifying the assessments to be done to confirm response to the induction chemotherapy given has been added • A section (8.1.2) clarifying the timeline for some baseline assessments has been added • Section 11 (previously Drug supply), now 'Drug supply and accountability', gives more information on keeping appropriate records on the trial drugs • Section 18 (Pharmacovigilance) of the protocol has been updated to include various current information on the reporting of Serious Adverse Events, pregnancies and their processing at UCL CTC • Section 18.3 – Clinical Review has been removed • Section 18.6 (previously Annual Safety Report(ASRs)), has now been updated to 'Development Safety Update Reports (DSURs)' • Section 21 (Trial monitoring and oversight) has been updated to reflect the current monitoring and oversight for the trial. • Section 24.6 – sponsorship details have been updated • Appendix 5 (Expected Adverse Events) – the AEs listed have been changed from 'for the Treatment Regimen' to 'for Allogeneic Transplants'. These changes have been made to clarify some information in the protocol and also to make some baseline assessments timelines compatible with local procedures and time frames.

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.

Non-serious AEs includes serious and non-serious AEs. Threshold for reporting = >5% Occurrences all is the number of subjects affected since worst grade was reported by sites

Notes: