Clinical trial results:
A Randomised Trial of the FLAMSA-BU Conditioning Regimen in Patients with Acute Myeloid Leukaemia and Myelodysplasia Undergoing Allogeneic Stem Cell Transplantation

Summary

EudraCT number	2012-005538-12
Trial protocol	GB
Global end of trial date	18 August 2020

Results information

Result version number	v1 (current)
This version publication date	23 January 2022
First version publication date	23 January 2022

Trial information

Trial identification

Sponsor protocol code	RG_12-264(HM2052)

Additional study identifiers

ISRCTN number	ISRCTN50855000
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Research Support Group, Aston Webb, B Block , Birmingham, United Kingdom, B15 2TT, Birmingham, United Kingdom, B15 2TT
Public contact	FIGARO Trial Coordinator, University of Birmingham, 004401213714365, IGARO Trial Coordinator, University of Birmingham, 004401213714365, 0044 01213714365, FIGARO@trials.bham.ac.uk
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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	25 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principal objective of the trial is to determine whether there is a difference in the overall survival (OS) of patients with high risk AML/MDS after a FLAMSA-BU transplant compared with patients receiving one of the three currently used transplant regimens (FMA/FBA/FB-ATG).

Protection of trial subjects:

Busulphan at the recommended dose and schedule is associated with profound myelosuppression. Severe
granulocytopenia, thrombocytopenia, anaemia, or any combination thereof may develop. Frequent complete
blood counts, including differential white blood cell counts, and platelet counts will be monitored during the
treatment and until recovery is achieved.
During periods of mylosuppression, prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) will be
adopted for the prevention and management of infections during the neutropenic period. Platelet and red blood
cell support, as well as the use of growth factors such as granulocyte colony stimulating factor (G-CSF), will be
employed as medically indicated.
Busulphan has not been studied in patients with hepatic impairment. Since busulphan is mainly metabolised
through the liver we will continue to monitor serum transaminase, alkaline phosphatase, and bilirubin regularly
for 28 days following transplant for early detection of hepatotoxicity. Only patients with adequate hepatic
function will be enrolled into the trial.
Hepatic veno-occlusive disease is a major complication that can occur during treatment with busulphan.
Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or
prior stem cell transplant may be at an increased risk. We will therefore monitor such patients closely.
No patients treated in clinical trials have yet experienced cardiac tamponade or other specific cardiac toxicities
related to busulphan. However cardiac function will be monitored closely in the immediate transplant period.
Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis has been reported in busulphan studies in one patient who died, although, no
clear aetiology was identified. In addition, busulphan might induce pulmonary toxicity that may be additive to
the effects produc

Background therapy: -

Evidence for comparator:

Transplant regimens selected for high risk AML and MDS patients vary across transplant centres in the UK and there is no clear consensus concerning the optimum transplant regimen. The control arm for this trial has been designed to include the three most commonly used RIC regimens currently used in the UK in this patient population.

Fludarabine/Melphalan/Alemtuzumab (FMA):

The Fludarabine/Melphalan/Alemtuzumab (FMA) RIC regimen has been used extensively in the UK for the treatment of patients with AML and MDS in whom a standard myeloablative transplant is contraindicated. The use of melphalan in conditioning for allogeneic SCT is based on its antitumour activity in a number of haematological malignancies in addition to its immunosuppressive effects24,25. Furthermore, fludarabine is a potent immunosuppressive agent that has potential synergistic activity with alkylators26. T cell depletion using alemtuzumab has been used in combination with fludarabine and melphalan to reduce the incidence of severe GvHD10. Studies have shown 3 year OS rates and DFS rates of 41% and 37% respectively using this transplant regimen8. However, in patients with relapsed/refractory AML at the time of transplant, the 3 year DFS is substantially reduced to 20%11. Separate studies have also indicated a poorer transplant outcome in patients with high risk disease.

Fludarabine/Busulphan/Alemtuzumab (FBA):

The combination of busulphan with fludarabine as conditioning therapy has been associated with significant clinical activity with OS rates of 30% at 2 years have been reported in patients with high risk AML or MDS27.

A retrospective analysis comparing fludarabine/busulphan versus fludarabine/melphalan based transplant conditioning revealed that the melphalan group was associated with a higher rate of non-relapse mortality and had a more intense myelosuppressive effect. However, survival rates in the busulphan group were not improved due to the higher rates of disease relapse s

Actual start date of recruitment	01 June 2013
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: 244
Worldwide total number of subjects	244
EEA total number of subjects	0

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)	183
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

244 patients with AML or MDS who were clinically indicated to receive a RIC allograft were recruited between Sept 2013 to Feb 2017 (164 AML, 80 MDS)

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient randomisation in order to confirm eligibility.
Screening assessments included: medical history, height, weight, demographic data, blood tests, clinical and cardiac assessments, ECOG performance, pregnancy test and bone marrow samples for research.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Sites could choose which control arm they wanted to use either;
Fludarabine/Melphalan/Alemtuzumab (FMA)
Fludarabine/busulphan/alemtuzumab (FBA)
Fludarabine/busulphan/ATG (FB-ATG)

Arm type	Active comparator
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

30mg/m2 once a day IV for 5 days

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 use

Dosage and administration details:

140mg/m2 once a day for one day

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

Dosage and administration details:

3.2mg.kg once daily for 2 days

Arm title	Experimental

Arm description:

FLAMSA-BU

Arm type	Experimental

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 30mg/m2 6 days	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 2g/m2 once daily for 4 days	
Investigational medicinal product name	Amsacrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100mg/m2 once a day for 4 days	
Investigational medicinal product name	Busulphan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 3.2mg/kg once a day for 4 days	

Number of subjects in period 1	Control	Experimental
Started	122	122
Completed	122	122

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)
Reporting group description:	
Overall Trial	

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	244	244	
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)	183	183	
From 65-84 years	61	61	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	59		
standard deviation	± 2	-	
Gender categorical			
Units: Subjects			
Female	99	99	
Male	145	145	
Underlying Disease AML			
Units: Subjects			
AML FMA/FBA/FB-ATG	140	140	
FLAMSA-BU	104	104	
Cytogenetic risk Control - AML			
Units: Subjects			
Adverse risk	50	50	
Intermediate Risk	105	105	
Favourable Risk	89	89	
Cytogenetic risk Experimental - AML			
Units: Subjects			
Adverse risk	50	50	
Intermediate risk	105	105	
Favourable risk	89	89	
Cytogenetic risk control - MDS			
Units: Subjects			
Good risk	105	105	
Intermediate risk	69	69	
Poor risk	70	70	

Cytogenetic risk experimental - MDS Units: Subjects			
Good risk	127	127	
Intermediate risk	45	45	
Poor risk	72	72	
Disease status (AML only) control Units: Subjects			
CR1/CR2	155	155	
Primary refractory	89	89	
Disease status (AML only) experimental Units: Subjects			
CR1/CR2	155	155	
Primary refractory	89	89	
Donor type control Units: Subjects			
Sibling	49	49	
Unrelated	195	195	
Donor type experimental Units: Subjects			
Sibling	49	49	
Unrelated	195	195	
MRD results control Units: Subjects			
Positive	81	81	
Negative	95	95	
Inadequate	27	27	
Unknown	41	41	
MRD results experimental Units: Subjects			
Positive	81	81	
Negative	95	95	
Inadequate	27	27	
Unknown	41	41	
IPSS (MDS only) experimental Units: Subjects			
Standard risk (<=2)	166	166	
High risk (>2)	78	78	
IPSS (MDS only) control Units: Subjects			
Standard risk (<=2)	166	166	
High (>2)	78	78	
HCT-CI control Units: Subjects			
<=2	145	145	
>=3	51	51	
Unknown	48	48	
HCT-CI experimental Units: Subjects			
<=2	145	145	
>=3	51	51	
Unknown	48	48	

FLT3 control Units: Subjects			
Absent	101	101	
Present	43	43	
Unknown	100	100	
FLT3 experimental Units: Subjects			
Absent	101	101	
Present	43	43	
Unknown	100	100	
NPM1 control Units: Subjects			
Absent	103	103	
Present	40	40	
Unknown	101	101	
NPM1 experimental Units: Subjects			
Absent	103	103	
Present	40	40	
Unknown	101	101	
Stem cell source control Units: Subjects			
Peripheral blood	208	208	
Bone marrow	36	36	
Stem cell source experimental Units: Subjects			
Peripheral blood	208	208	
Bone marrow	36	36	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Sites could choose which control arm they wanted to use either; Fludarabine/Melphalan/Alemtuzumab (FMA) Fludarabine/busulphan/alemtuzumab (FBA) Fludarabine/busulphan/ATG (FB-ATG)	
Reporting group title	Experimental
Reporting group description:	
FLAMSA-BU	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
Calculated as the time from date of randomisation to the date of death from any cause, or date last seen for censored patients who are still alive at the end of follow-up.	
End point type	Primary
End point timeframe:	
OS (defined as the time from date of randomisation to the date of death from any cause) on both an intention-to-treat (ITT)	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	122		
Units: OS				
number (not applicable)				
Two year	58.8	60.9		
Three year	52.9	55.4		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Therefore assuming a 2 year OS in the control arm (FMA/FBA) of 25%, in order to detect a 15% improvement in the experimental arm (FLAMSA-BU), a total of about 214 patients (2 sided α=0.15, β=0.16) were required. In order to account for the 10% of patients in the trial who are randomised but do not undergo transplant, the trial aimed to recruit around 240 patients on a 1:1 basis.	
Comparison groups	Experimental v Control

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.5
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
Variability estimate	Standard deviation

Secondary: Event free survival

End point title	Event free survival

End point description:

For patients randomised in CR1/CR2 - calculated as the time fro date of randomisation to the first date of relapse or death from any cause, or date last seen for censored patients who have not had an event by the end of follow-up.

End point type	Secondary

End point timeframe:

Event free survival (EFS) (defined for patients randomised in CR1/CR2 as the time from date of randomisation to the first of date of relapse or death from any cause and for patients with primary refractory disease as the time from date of randomisation

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	122		
Units: EFS				
number (not applicable)				
2 years	48.7	54.6		
3 years	44.8	49.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of disease relapse

End point title	Cumulative incidence of disease relapse

End point description:

Cumulative incidence of disease relapse is defined as time in days from date of randomisation to date of disease relapse. Death will be considered a competing risk with time being calculated as date of randomisation to date of death and patients who do not experience disease relapse or death being censored at their date last. Primary refractory patients will be excluded from this analysis.

End point type	Secondary

End point timeframe:

Time in days form date of randomisation to date of disease relapse

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	122		
Units: CIR				
number (not applicable)				
I year	21.8	19.8		
2 year	29.4	26.4		
3 year	32.4	30.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Transplant related mortality

End point title	Transplant related mortality

End point description:

Cumulative incidence of TRM is defined with non-transplant related deaths as a competing risk, by the time in days from the date of randomisation to date of any death unrelated to the underlying disease and considered related to the transplant procedure. Date of death will be taken for patients who experience a competing event (non-transplant related deaths) and date last seen for censored patients who have not experienced an event or competing event.
Table 34: TRM

End point type	Secondary

End point timeframe:

Day 100 and 12 months TRM defined as as any death unrelated to the underlying disease and considered related to the transplant procedure

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	108		
Units: TRM				
number (not applicable)				
Day 100 TRM	2.8	13.9		
1 year TRM	16.8	20.5		
2 year TRM	18.7	21.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of graft versus host disease (GvHD)	
End point title	Incidence of graft versus host disease (GvHD)
End point description: • Incidence of GvHD	
End point type	Secondary
End point timeframe: Incidence of GvHD	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	39		
Units: aGvHD				
number (not applicable)				
Day 100 cumulative incidence grade 3-4 Day 100 cumulative incidence grade 2-4	1.7 10.1	5.8 8.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of graft versus host disease (GvHD)	
End point title	Incidence of graft versus host disease (GvHD)
End point description: Incidence of chronic GvHD	
End point type	Secondary
End point timeframe: Incidence of chronic GvHD	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	31		
Units: cGvHD				
number (not applicable)				
1 year cumulative incidence of cGvHD	25.2	17.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were to be documented and reported from the date of commencement of protocol defined treatment until 30 days after the date of transplant

Adverse event reporting additional description:

The collection and reporting of AEs were in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient with reference to the Investigator Brochure.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Control

Reporting group description: -

Reporting group title	Experimental

Reporting group description: -

Serious adverse events	Control	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 122 (9.02%)	29 / 122 (23.77%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	1	5	
General disorders and administration site conditions			
fever			
subjects affected / exposed	0 / 122 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	1 / 122 (0.82%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders other			
subjects affected / exposed	1 / 122 (0.82%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	3 / 3	
Myocardial infarction			
subjects affected / exposed	1 / 122 (0.82%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Intracranial hemorrhage			
subjects affected / exposed	1 / 122 (0.82%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder other			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Other			
subjects affected / exposed	0 / 122 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Febrile Neutropenia			
subjects affected / exposed	0 / 122 (0.00%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	3 / 3	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	3 / 122 (2.46%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oral pain			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	1 / 122 (0.82%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			

subjects affected / exposed	0 / 122 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Generalized muscle weakness			
subjects affected / exposed	1 / 122 (0.82%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Missing			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other			
subjects affected / exposed	1 / 122 (0.82%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infection. Diarrhea			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 122 (0.82%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 122 (54.10%)	89 / 122 (72.95%)	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	14 / 122 (11.48%)	16 / 122 (13.11%)	
occurrences (all)	30	40	
Neutrophil count decreased			
subjects affected / exposed	35 / 122 (28.69%)	37 / 122 (30.33%)	
occurrences (all)	78	56	
Platelet count decreased			
subjects affected / exposed	31 / 122 (25.41%)	38 / 122 (31.15%)	
occurrences (all)	77	158	
White blood cell count decreased			
subjects affected / exposed	25 / 122 (20.49%)	30 / 122 (24.59%)	
occurrences (all)	54	48	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 122 (17.21%)	32 / 122 (26.23%)	
occurrences (all)	29	73	

Febrile neutropenia			
subjects affected / exposed	24 / 122 (19.67%)	46 / 122 (37.70%)	
occurrences (all)	27	52	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 122 (9.02%)	17 / 122 (13.93%)	
occurrences (all)	11	18	
mucositis oral			
subjects affected / exposed	10 / 122 (8.20%)	16 / 122 (13.11%)	
occurrences (all)	10	16	
Nausea			
subjects affected / exposed	6 / 122 (4.92%)	11 / 122 (9.02%)	
occurrences (all)	9	11	
Infections and infestations			
Device related infection			
subjects affected / exposed	3 / 122 (2.46%)	10 / 122 (8.20%)	
occurrences (all)	3	10	
Other, specify			
subjects affected / exposed	7 / 122 (5.74%)	8 / 122 (6.56%)	
occurrences (all)	10	11	
Sepsis			
subjects affected / exposed	1 / 122 (0.82%)	12 / 122 (9.84%)	
occurrences (all)	1	12	
Metabolism and nutrition disorders			
Anorexia nervosa			
subjects affected / exposed	3 / 122 (2.46%)	11 / 122 (9.02%)	
occurrences (all)	3	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2013	Addition of FB-ATG regimen Patients should be randomised 2-6 weeks prior to transplant admission date Changes in scheduling solely for logistical reasons or to allow weekday administration of chemotherapy permitted without approval from CI or CC
11 April 2014	Addition of new inclusion criteria; Patients with Flt-3 ITD positive AML; Patients with persistent or rising MRD levels, who have a morphological CR; Patients who been have defined as high risk by MRD criteria Reclassification of T-cell depletion agents from IMPS to NIMPs
15 December 2014	Modification to guidance on Mycophenolate Mofetil Patients 60 years and over omit day -7 busulphan and count as a rest day Clarification of patients age range for the FLAMSA-Bu schedule
20 January 2015	Revised schedule for FLAMSA-BU conditioning regimen in patients 60 years and over. Exclusion criteria reworded to clarify the inclusion of patients who have had a previous malignancy and which also applies to those with a Sorror score of greater than 3 due to a previous malignancy
27 May 2015	Patients with Hep-B are now allowed to be included as the presence of the virus does not cause any issues with treatment. There is new wording in the patient information sheet to clarify the aim of the clinical trial and also to state that there may be some variation in the number of days for treatment depending on the local hospital schedules.
14 December 2015	to allow the inclusion of patients defined as patients not in complete remission (CR) after the first course of induction therapy and patients with secondary AML who have a previous history of myelodysplasia, antecedent haematological disease or chemotherapy exposure in CR1 or CR2. The classification of high risk patients defined according to the clinical trial AML 17 has been removed as the AML 17 trial is now closed. The stopping rule has been redefined on advice from the trial steering committee for the trial. This was based on the data obtained from the trial so far.
16 February 2018	Addition of Clatterbridge as a site
25 March 2019	Change of PI ate Leicester Royal Infirmary from Dr Ann Hunter to Dr Alexander Martin

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.

None reported

Notes: