



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 |
| Scientific contact | FIGARO Trial Coordinator, University of Birmingham, 004401213714365, FIGARO Trial Coordinator, University of Birmingham, 004401213714365, 0044 01213714365, FIGARO@trials.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 | 25 November 2021 |
| Is this the analysis of the primary completion data? | No |
| <hr/> | |
| 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 myelosuppression, 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 produced

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 effects^{24,25}. 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/m ² 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/m ² 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/m ² 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 $\alpha=0.15$, $\beta=0.16$) 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 from 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 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 from 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) | | | | |
| 1 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 | 1.7 | 5.8 | | |
| Day 100 cumulative incidence grade 2-4 | 10.1 | 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 occurrences (all) | 24 / 122 (19.67%) 27 | 46 / 122 (37.70%) 52 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 11 / 122 (9.02%) 11 | 17 / 122 (13.93%) 18 | |
| mucositis oral subjects affected / exposed occurrences (all) | 10 / 122 (8.20%) 10 | 16 / 122 (13.11%) 16 | |
| Nausea subjects affected / exposed occurrences (all) | 6 / 122 (4.92%) 9 | 11 / 122 (9.02%) 11 | |
| Infections and infestations | | | |
| Device related infection subjects affected / exposed occurrences (all) | 3 / 122 (2.46%) 3 | 10 / 122 (8.20%) 10 | |
| Other, specify subjects affected / exposed occurrences (all) | 7 / 122 (5.74%) 10 | 8 / 122 (6.56%) 11 | |
| Sepsis subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | 12 / 122 (9.84%) 12 | |
| Metabolism and nutrition disorders | | | |
| Anorexia nervosa subjects affected / exposed occurrences (all) | 3 / 122 (2.46%) 3 | 11 / 122 (9.02%) 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 have been 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 at 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: