



Clinical trial results:

Phase II Study of the Adjunctive Use of Azacitidine in Patients Undergoing Reduced Intensity Allogeneic Transplantation for Acute Myeloid Leukaemia

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2007-006475-36 |
| Trial protocol | GB |
| Global end of trial date | 31 January 2014 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 19 February 2020 |
| First version publication date | 19 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_07-187 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN36825171 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Vincent Drive, Birmingham, United Kingdom, B15 2TT |
| Public contact | CRCTU general enquires, University of Birmingham, crctu-generalenquiries@bham.ac.uk |
| Scientific contact | CRCTU general enquires, University of Birmingham, crctu-generalenquiries@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 | 22 January 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of Azacitidine in patients following reduced intensity conditioned allogeneic transplantation for AML.

Protection of trial subjects:

Specific dose modifications were recommended to decrease the incidence and relieve the symptoms of:

Grade 3 and 4 haematological toxicities

Grade 3/ and 4 non-haematological toxicities

The following rules were put in place:

If 3 out of the first 5 patients experience Grade 4 haematological toxicities which are deemed related to Azacitidine then Azacitidine will be reduced to a dose of 24mg/m² for all subsequent patients.

The trial will be stopped if 4 patients experience sustained Grade 4 haematological toxicities of more than 42 days or more than 4 recurring grade 3-4 non haematological toxicities deemed related to Azacitidine.

The trial will be stopped if more than 4 patients develop unexpected recurring non- haematological Grade 3-4 toxicities deemed related to Azacitidine

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 24 July 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 51 |
| Worldwide total number of subjects | 51 |
| EEA total number of subjects | 51 |

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) | 39 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 8 UK sites between 24-Jul-2008 and 05-Oct-2011.

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient registration in order to confirm eligibility.

All patients had a full medical, disease and drug therapy history, pre-transplant bone marrow.

Patients who were unfit to receive Azacitadine following transplant did not begin trial treatment and so, did not reach the baseline period.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 51 |
| Number of subjects completed | 37 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 3 |
| Reason: Number of subjects | Ineligible: 2 |
| Reason: Number of subjects | Suffered Acute GvHD: 1 |
| Reason: Number of subjects | Infection: 8 |

Period 1

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

Arms

| | |
|--|-------------------------------------|
| Arm title | Azacitadine treatment |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Azacitidine |
| Investigational medicinal product code | |
| Other name | Vidaza |
| Pharmaceutical forms | Powder for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

36 mg/m² sc x 5 days every 28 days commenced on week 6 post transplant for 10 cycles.

| Number of subjects in period 1 ^[1] | Azacitadine treatment |
|---|-----------------------|
| Started | 37 |
| Completed | 16 |
| Not completed | 21 |
| Physician decision | 1 |

| | |
|--------------------------|---|
| Relapse | 9 |
| Adverse event, non-fatal | 9 |
| Not reported | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The protocol defines evaluable patients as those who commenced at least 1 cycle of Azacitidine. Not all of the patients that were registered to the trial started Azacitidine treatment, so only those that did are included in the baseline period.

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 37 | 37 | |
| 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) | 30 | 30 | |
| From 65-84 years | 7 | 7 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 21 | |
| Male | 16 | 16 | |
| Diagnosis | | | |
| Units: Subjects | | | |
| AML - de novo | 24 | 24 | |
| AML - secondary | 13 | 13 | |
| Karyotype | | | |
| Units: Subjects | | | |
| Intermediate | 30 | 30 | |
| Poor | 7 | 7 | |
| Disease status | | | |
| Units: Subjects | | | |
| First complete remission (CR1) | 24 | 24 | |
| Second Complete Remission (CR2) | 8 | 8 | |
| First relapse | 3 | 3 | |
| Primary refractory disease | 2 | 2 | |
| Conditioning Treatment | | | |
| Units: Subjects | | | |
| Fludarabine, Melphalan, Campath (FMC) | 34 | 34 | |
| Fludarabine, Cytarabine, Amsacrine (FLAMSA) | 3 | 3 | |
| Donor Type | | | |
| Units: Subjects | | | |
| Identical sibling | 12 | 12 | |
| Mismatched relative | 1 | 1 | |
| Mismatched unrelated donor | 1 | 1 | |

| | | | |
|----------------------------|----|----|--|
| Matched unrelated donor | 23 | 23 | |
| CMV status (patient/donor) | | | |
| Units: Subjects | | | |
| positive/positive | 14 | 14 | |
| positive/negative | 6 | 6 | |
| negative/positive | 3 | 3 | |
| negative/negative | 14 | 14 | |
| Stem cell source | | | |
| Units: Subjects | | | |
| Peripheral Blood | 34 | 34 | |
| Bone Marrow | 3 | 3 | |

End points

End points reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Azacitadine treatment |
|-----------------------|-----------------------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

Primary: Tolerability of Azacitidine post transplant

| | |
|-----------------|--|
| End point title | Tolerability of Azacitidine post transplant ^[1] |
|-----------------|--|

| |
|------------------------|
| End point description: |
|------------------------|

| |
|---|
| Tolerability is defined as the number of patients completing treatment. |
|---|

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|-----------------|
| Post transplant |
|-----------------|

| |
|--------|
| Notes: |
|--------|

| |
|---|
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |
|---|

| |
|--|
| Justification: No formal statistical analyses were performed. The protocol states that 'All analysis will be descriptive'. |
|--|

| End point values | Azacitadine treatment | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Patients | | | | |
| Tolerated treatment | 30 | | | |
| Did not tolerate treatment | 7 | | | |

Statistical analyses

| |
|--|
| No statistical analyses for this end point |
|--|

Secondary: Relapse Free Survival

| | |
|-----------------|-----------------------|
| End point title | Relapse Free Survival |
|-----------------|-----------------------|

| |
|------------------------|
| End point description: |
|------------------------|

| |
|---|
| Relapse free survival at one year post-transplant and two years post-transplant |
|---|

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|--------------------|
| One year, Two year |
|--------------------|

| | | | | |
|----------------------------------|-----------------------|--|--|--|
| End point values | Azacitadine treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: RFS | | | | |
| number (confidence interval 95%) | | | | |
| 1 year RFS (%) | 56.8 (42.8 to 75.2) | | | |
| 2 year RFS (%) | 48.6 (34.9 to 67.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|------------------------|------------------|
| End point title | Overall survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| One year, two year | |

| | | | | |
|----------------------------------|-----------------------|--|--|--|
| End point values | Azacitadine treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: OS | | | | |
| number (confidence interval 95%) | | | | |
| 1 year OS (%) | 80.6 (68.7 to 94.6) | | | |
| 2 year OS (%) | 49.6 (35.6 to 69.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Graft versus Host Disease (Acute)

| | |
|------------------------|-----------------------------------|
| End point title | Graft versus Host Disease (Acute) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post transplant | |

| End point values | Azacitadine treatment | | | |
|-------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Patients | | | | |
| Did not experience acute GvHD | 20 | | | |
| Experienced grade 1 or 2 acute GvHD | 17 | | | |
| Experienced grade 3 or 4 acute GvHD | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Graft versus Host Disease (Chronic)

| | |
|------------------------|-------------------------------------|
| End point title | Graft versus Host Disease (Chronic) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-transplant | |

| End point values | Azacitadine treatment | | | |
|------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Patients | | | | |
| Did not experience Chronic GvHD | 30 | | | |
| Experienced limited chronic GvHD | 7 | | | |
| Experienced extensive chronic GvHD | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Chimerism (Whole blood)

| | |
|-------------------------|-------------------------|
| End point title | Chimerism (Whole blood) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 90 days post-transplant | |

| End point values | Azacitadine treatment | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Patients | | | | |
| Full | 22 | | | |
| Mixed | 15 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Chimerism (T-cell)

| | |
|-----------------|--------------------|
| End point title | Chimerism (T-cell) |
|-----------------|--------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

90 days post-transplant

| End point values | Azacitadine treatment | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Patients | | | | |
| Full | 7 | | | |
| Mixed | 30 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the start of Azacitidine treatment until 28 days after the last dose of Azacitidine or until the start of other anti-cancer therapy – whichever occurs first

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Azacitidine treatment |
|-----------------------|-----------------------|

Reporting group description:

All patients who received Azacitidine treatment

| Serious adverse events | Azacitidine treatment | | |
|---|-----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 37 (40.54%) | | |
| number of deaths (all causes) | 19 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Creatinine increased | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations - Other, Abnormal ALT | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences causally related to treatment / all | 1 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomitting | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnea | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and Subcutaneous tissue disorders - Other, Rash | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders - Other, Shingles | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Bladder infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations - Other, Chest infection | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin infection | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and Infestations - Other, CMV | | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and Infestations - Other, H. influenzae | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and Infestations - Other, Para influenza | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and Infestations - Other, Shingles | | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|--|----------------|--|--|
| Infections and infestations - Other, Staphylococcus aureus | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Azacitadine treatment | | |
|---|-----------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 37 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Edema limbs | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences (all) | 4 | | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 37 (32.43%) | | |
| occurrences (all) | 23 | | |
| Fever | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | | |
| occurrences (all) | 14 | | |
| Injection site reaction | | | |
| subjects affected / exposed | 25 / 37 (67.57%) | | |
| occurrences (all) | 64 | | |
| Lethargy | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | | |
| occurrences (all) | 7 | | |

| | | | |
|--|---|--|--|
| Pain subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 4 / 37 (10.81%) 4 10 / 37 (27.03%) 12 | | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | | |
| Investigations Alkaline phosphatase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Hemoglobin increased subjects affected / exposed occurrences (all) Hyperkalemia subjects affected / exposed occurrences (all) Hypermagnesemia subjects affected / exposed occurrences (all) Investigations - Other, Decreased calcium subjects affected / exposed occurrences (all) Neutrophil count decreased | 4 / 37 (10.81%) 12 3 / 37 (8.11%) 5 5 / 37 (13.51%) 7 6 / 37 (16.22%) 18 3 / 37 (8.11%) 3 2 / 37 (5.41%) 4 | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 14 / 37 (37.84%) | | |
| occurrences (all) | 52 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 24 / 37 (64.86%) | | |
| occurrences (all) | 113 | | |
| White blood cell decreased | | | |
| subjects affected / exposed | 13 / 37 (35.14%) | | |
| occurrences (all) | 119 | | |
| Creatinine increased | | | |
| subjects affected / exposed | 15 / 37 (40.54%) | | |
| occurrences (all) | 36 | | |
| Investigations - Other, Decreased magnesium | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 10 | | |
| Investigations - Other, Decreased sodium | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 6 | | |
| Investigations - Other, Decreased urea | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 5 | | |
| Investigations - Other, Increased CRP | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | | |
| occurrences (all) | 28 | | |
| Investigations - Other, Increased LDH | | | |
| subjects affected / exposed | 7 / 37 (18.92%) | | |
| occurrences (all) | 19 | | |
| Investigations - Other, Increased urea | | | |
| subjects affected / exposed | 9 / 37 (24.32%) | | |
| occurrences (all) | 41 | | |
| Investigations - Other, Increased WCC | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 10 | | |

| | | | |
|--------------------------------------|-----------------------------|------------------|--|
| Nervous system disorders | Headache | | |
| | subjects affected / exposed | 9 / 37 (24.32%) | |
| | occurrences (all) | 9 | |
| | Neuralgia | | |
| | subjects affected / exposed | 2 / 37 (5.41%) | |
| | occurrences (all) | 2 | |
| | Tremor | | |
| | subjects affected / exposed | 2 / 37 (5.41%) | |
| | occurrences (all) | 2 | |
| | | | |
| | | | |
| | | | |
| Blood and lymphatic system disorders | Anemia | | |
| | subjects affected / exposed | 23 / 37 (62.16%) | |
| | occurrences (all) | 119 | |
| Eye disorders | Dry eye | | |
| | subjects affected / exposed | 2 / 37 (5.41%) | |
| | occurrences (all) | 2 | |
| Gastrointestinal disorders | Abdominal pain | | |
| | subjects affected / exposed | 4 / 37 (10.81%) | |
| | occurrences (all) | 5 | |
| | Diarrhoea | | |
| | subjects affected / exposed | 21 / 37 (56.76%) | |
| | occurrences (all) | 36 | |
| | Mucositis oral | | |
| | subjects affected / exposed | 4 / 37 (10.81%) | |
| | occurrences (all) | 5 | |
| | Nausea | | |
| | subjects affected / exposed | 23 / 37 (62.16%) | |
| | occurrences (all) | 46 | |
| | Vomiting | | |
| | subjects affected / exposed | 12 / 37 (32.43%) | |
| | occurrences (all) | 20 | |
| | Constipation | | |
| | subjects affected / exposed | 4 / 37 (10.81%) | |
| | occurrences (all) | 5 | |

| | | | |
|---|--|--|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Dry skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 37 (5.41%)</p> <p>2</p> <p>Skin infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Rash maculo-papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 37 (5.41%)</p> <p>2</p> <p>Skin and subcutaneous tissue disorders - Other, Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>7 / 37 (18.92%)</p> <p>13</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 37 (5.41%)</p> <p>2</p> | | | |
| <p>Infections and infestations</p> <p>Mucosal infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Upper respiratory infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Skin infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 37 (8.11%)</p> <p>3</p> <p>Infections and infestations - other, Chest infection</p> | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 9 | | |
| Infections and infestations - Other, CMV | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations - Other, HSV | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations - Other, Infection | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations - Other, Para influenza | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations - Other, Rhinovirus | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations - Other, Shingles | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 3 | | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences (all) | 4 | | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| hypocalcemia | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | | |
| occurrences (all) | 19 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Hypokalemia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | | |
| occurrences (all) | 19 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | | |
| occurrences (all) | 27 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 30 June 2008 | An inclusion criterion was amended to remove an upper age limit for patient entry to the study. <ul style="list-style-type: none">• The timeframe for patients to consent to the trial was extended• The contact details of staff managing the trial was amended• The patient information sheet (PIS) was amended to show the different time frame for consenting to the trial.• Addition of two new participating sites |
| 17 October 2008 | The PIS was amended to clarify that patients may have anonymised data sent to Celgene Corporation (who manufacture and supply the IMP) as part of their ongoing monitoring of the safety and activity of their agent. A revised consent form was sent to the Ethics board on 23rd Feb 2009 as the reference to the patient information sheet was incorrect. |
| 12 April 2009 | <ul style="list-style-type: none">• Addition of a participating site• Inclusion criteria amended to allow inclusion of patients who undergo reduced intensity conditioned transplantation using an alternative chemotherapy (FLAMSA) regimen• Patients who have not recovered sufficiently after transplant to receive azacitidine (the IMP) by 6 months to be withdrawn from the trial.• Protocol amended to allow patients who have active non-life-threatening infection can receive azacitidine provided the blood counts are stable and meet the entry criteria for commencing azacitidine |
| 30 April 2009 | Myelodysplasia (MDS) patients were removed from the eligibility criteria <ul style="list-style-type: none">• Blood samples required for immune studies were reduced• Criteria to assess renal function were also added. |
| 04 November 2009 | Change of Principal Investigator at Christie Hospital Foundation NHS Trust, Manchester |
| 11 January 2011 | <ul style="list-style-type: none">• Planned recruitment was clarified to include 40 evaluable patients which was defined as patients commencing with least 1 cycle of azacitidine• Single allele mismatches defined to include RICAZA_Final_Clinical_Study_Report Version 1.0_29-May-2015 HLA-A, HLA-B, HLA-C, HLA-DRB1• Addition of wording: No dose interruptions will be performed for grades 1 and 2 nonhaematological toxicities• Further guidance given on dose modifications for grade 3 haematological toxicities• Storage conditions for azacitidine amended• Serious Adverse Event (SAE) definition updated• Wording added to reflect that SAE and Suspected Unexpected Serious Adverse Reaction (SUSAR) information will be sent to Celgene |
| 14 March 2011 | <ul style="list-style-type: none">• IMP label updated with new storage conditions• PIS was updated so that patients were aware what patient related data is accessible to 3rd parties and what type of information is passed on.• Addition of a Release of Medical Information Form and Consent Form to be used in relation to pregnancy notifications during the trial |
| 21 June 2011 | Amendment submitted to request the use of commercial stock of azacitidine for one dose to be given to a trial patient |
| 21 December 2011 | Addition of a participating site |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22234690>

<http://www.ncbi.nlm.nih.gov/pubmed/26363443>