# Clinical trial results:
# Clinical phase II trial to describe the safety and efficacy of Treosulfan-based conditioning therapy prior to allogeneic haematopoietic stem cell transplantation in paediatric patients with haematological malignancies

## Summary

| | |
|---|---|
| EudraCT number | 2013-003604-39 |
| Trial protocol | DE PL AT CZ GB IT |
| Global end of trial date | |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 02 May 2018 |
| First version publication date | 02 May 2018 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | MC-FludT.17/M |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02333058 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | medac Gesellschaft für klinische Spezialpräparate mbH |
| Sponsor organisation address | Theaterstraße 6, Wedel, Germany, 22880 |
| Public contact | Clinical Trial Disclosure Desk, medac GmbH, 0049 410380060, eudract@medac.de |
| Scientific contact | Medical Expert, medac GmbH, 0049 410380060, med-wiss@medac.de |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000883-PIP01-10 |
| 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 | Interim |
| Date of interim/final analysis | 13 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 September 2017 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

To describe the safety and efficacy of i.v. Treosulfan administered as part of a standardised Fludarabine-containing conditioning and to contribute to a pharmacokinetic (PK) model which permits - in conjunction with data comparing Treosulfan and Busulfan in adults with malignant diseases - to extend the use of Treosulfan in the paediatric population by extrapolating efficacy.

Protection of trial subjects:

The DMC reviewed all available safety and efficacy data frequently at least every 6 months.
PK blood sampling was performed only in a subset of trial subjects. A sparse sampling concept was used.
Subjects’s data were transferred pseudonymously.

Background therapy:

This trial protocol allowed administration of two different background conditioning regimens with Treosulfan :
1. Standard regimen A: Fludarabine i.v. (30 mg/m²/day)
2. Intensified regimen B: Fludarabine i.v. (30 mg/m²/day) plus ThioTEPA i.v. (2 x 5 mg/kg/day)

The investigator decided for each individual patient whether to treat the patient with regimen A or with regimen B.

Evidence for comparator:

NA

| | |
|---|---|
| Actual start date of recruitment | 01 July 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Regulatory reason |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 37 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Germany: 20 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Worldwide total number of subjects | 70 |
| EEA total number of subjects | 70 |

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) | 9 |
| Children (2-11 years) | 28 |
| Adolescents (12-17 years) | 33 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects fulfilled the criteria to be involved in the trial. According to GCP and the national regulations written informed consent was obtained from parent(s), legal guardian(s) or - if required by national law - by the subject. Informed assent was obtained from subjects.

### Pre-assignment

Screening details:

No study specific screening phase was planned in this trial. All paediatric patients were routinely checked for their general eligibility for an allo-HSCT procedure. All examinations are part of routine care and are not considered study specific procedures.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline up to 12 month (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Treosulfan |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Treosulfan |
| Investigational medicinal product code | NA |
| Other name | Ovastat 1000, Treosulfan for injection, L-Threitol 1,4-bis(methanesulfonate) |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patients were treated with BSA adapted Treosulfan doses. The treatment consists of 10 g/m² Treosulfan for patients with a BSA ≤ 0.5 m², 12 g/m² Treosulfan for a BSA > 0.5 to 1.0 m² or 14 g/m² Treosulfan for a BSA > 1.0 m² administered on three consecutive days (Days - 6, -5, -4).

| **Number of subjects in period 1** | Treosulfan |
|---|---|
| Started | 70 |
| Completed | 63 |
| Not completed | 7 |
| Adverse event, serious fatal | 1 |
| Death | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Treosulfan |

Reporting group description: -

| Reporting group values | Treosulfan | Total | |
|---|---|---|---|
| Number of subjects | 70 | 70 | |
| Age categorical<br>Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 9 | 9 | |
| Children (2-11 years) | 28 | 28 | |
| Adolescents (12-17 years) | 33 | 33 | |
| Age continuous<br>Units: years | | | |
| median | 9.5 | | |
| full range (min-max) | 0 to 17 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 44 | 44 | |
| Disease<br>Units: Subjects | | | |
| ALL - acute lymphoblastic leukaemia | 27 | 27 | |
| AML - acute myeloid leukaemia | 29 | 29 | |
| MDS - myelodysplastic syndrome | 10 | 10 | |
| JMML - juvenile myelomonocytic leukaemia | 4 | 4 | |
| Number of HSCT<br>Units: Subjects | | | |
| First | 65 | 65 | |
| Second | 5 | 5 | |
| Donor type<br>Units: Subjects | | | |
| MSD - matched sibling donor | 13 | 13 | |
| MFD - matched family donor | 1 | 1 | |
| MUD - matched unrelated donor | 56 | 56 | |
| BSA - Body surface area<br>Units: m² | | | |
| median | 1.10 | | |
| full range (min-max) | 0.32 to 2.00 | - | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Treosulfan |
| Reporting group description: - | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set is equal to the Safety Analysis Set. | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety Analysis Set includes all subjects enrolled in the trial who have received at least one dose of Treosulfan. | |

### Primary: Freedom from TRM - number

| | |
|---|---|
| End point title | Freedom from TRM - number[1] |
| End point description: | |
| Freedom from transplant (treatment) - related mortality until day +100 - number of subjects with and without event | |
| End point type | Primary |
| End point timeframe: | |
| Until day +100 after HSCT | |

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 statistical analysis for comparison has been performed because this trial consists only of one treatment arm.

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| Without TRM | 69 | | | |
| With TRM | 1 | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Freedom from TRM - rate

| | |
|---|---|
| End point title | Freedom from TRM - rate[2] |
| End point description: | |
| Freedom from transplant (treatment) - related mortality until day +100 - percentage of subjects without transplant (treatment) - related death | |
| End point type | Primary |
| End point timeframe: | |
| Until day +100 after HSCT | |

Notes:

[2] - 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 statistical analysis for comparison has been performed because this trial consists only of one treatment arm.

| **End point values** | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 98.6 (93.4 to 99.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Engraftment of neutrophils - number

| End point title | Engraftment of neutrophils - number |
|---|---|
| End point description: | |
| Engraftment of neutrophils - number of subjects with and without event | |
| End point type | Secondary |
| End point timeframe: | |
| Until day +100 after HSCT | |

| **End point values** | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 69 | | | |
| Without event | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Engraftment of neutrophils - conditional cumulative incidence

| End point title | Engraftment of neutrophils - conditional cumulative incidence |
|---|---|
| End point description: | |
| Engraftment of neutrophils - conditional cumulative incidence | |
| End point type | Secondary |
| End point timeframe: | |
| Until day +100 after HSCT | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 100.00 (97.7 to 100.0) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - number

| End point title | Incidence of complete donor type chimerism - number |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Day +28 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Day +28 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: subjects | | | | |
| With complete chimerism | 65 | | | |
| Without complete chimerism | 3 | | | |
| Without information | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - rate

| End point title | Incidence of complete donor type chimerism - rate |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Day +28 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Day +28 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 94.2 (87.2 to 98.0) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - number

| End point title | Incidence of complete donor type chimerism - number |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Day +100 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Day +100 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: subjects | | | | |
| With complete chimerism | 63 | | | |
| Without complete chimerism | 6 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - rate

| End point title | Incidence of complete donor type chimerism - rate |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Day +100 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Day +100 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 91.3 (83.6 to 96.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - number

| End point title | Incidence of complete donor type chimerism - number |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Month 12 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Month 12 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: subjects | | | | |
| With complete chimerism | 52 | | | |
| Without complete chimerism | 3 | | | |
| Without information | 2 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of complete donor type chimerism - rate

| End point title | Incidence of complete donor type chimerism - rate |
|---|---|
| End point description: | |
| Incidence of complete donor type chimerism at visit Month 12 | |
| End point type | Secondary |
| End point timeframe: | |
| Visit Month 12 | |

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 57 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 91.2 (82.4 to 96.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Non-relapse mortality - number

| End point title | Non-relapse mortality - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 2 | | | |
| Without event | 68 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Non-relapse mortality - cumulative incidence

| End point title | Non-relapse mortality - cumulative incidence |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 1.4 (0.0 to 3.8) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Primary graft failure - number

| End point title | Primary graft failure - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: event | | | | |
| Yes | 0 | | | |
| No | 70 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Primary graft failure - rate

| End point title | Primary graft failure - rate |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 0.0 (0.0 to 4.2) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Secondary graft failure - number

| End point title | Secondary graft failure - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: events | | | | |
| Yes | 1 | | | |
| No | 68 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Secondary graft failure - rate

| End point title | Secondary graft failure - rate |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 1.4 (0.1 to 6.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of relapse/progression - number

| End point title | Incidence of relapse/progression - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 11 | | | |
| Without event | 59 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of relapse/progression - cumulative incidence

| End point title | Incidence of relapse/progression - cumulative incidence |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 15.7 (8.6 to 22.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Relapse/progression-free survival - number

| End point title | Relapse/progression-free survival - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 13 | | | |
| Without relapse/progression or death | 57 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Relapse/progression-free survival - rate

| End point title | Relapse/progression-free survival - rate |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 82.7 (73.6 to 88.9) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival - number

| End point title | Overall survival - number |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| Dead | 7 | | | |
| Alive | 63 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival - rate

| End point title | Overall survival - rate |
|---|---|

End point description:

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

End point timeframe:

Until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 91.4 (83.9 to 95.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Acute GvHD grade I-IV - number

| End point title | Acute GvHD grade I-IV - number |
|---|---|

End point description:

Acute graft versus host disease of grades I to IV - number of subjects with and without event

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

End point timeframe:

Until 100 days after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 30 | | | |
| Without event | 40 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Acute GvHD grade I-IV - cumulative incidence

| End point title | Acute GvHD grade I-IV - cumulative incidence |
|---|---|

End point description:

Acute graft versus host disease of grades I to IV - cumulative incidence

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

End point timeframe:

Until 100 days after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 43.5 (33.7 to 53.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Acute GvHD grade III-IV - number

| End point title | Acute GvHD grade III-IV - number |
|---|---|

End point description:

Acute graft versus host disease of grades III to IV - number of subjects with and without event

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

End point timeframe:

Until 100 days after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: subjects | | | | |
| With event | 6 | | | |
| Without event | 64 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Acute GvHD grade III-IV - cumulative incidence

| End point title | Acute GvHD grade III-IV - cumulative incidence |
|---|---|

End point description:

Acute graft versus host disease of grades III to IV - cumulative incidence

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

End point timeframe:

Until 100 days after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 70 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 8.7 (3.1 to 14.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Chronic GvHD - number

| End point title | Chronic GvHD - number |
|---|---|

End point description:

Chronic graft versus host disease - number of subjects with and without event

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

End point timeframe:

From 100 days after HSCT until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: subjects | | | | |
| With event | 17 | | | |
| Without event | 50 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Chronic GvHD - cumulative incidence

| End point title | Chronic GvHD - cumulative incidence |
|---|---|

End point description:

Chronic graft versus host disease - cumulative incidence

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

End point timeframe:

From 100 days after HSCT until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 24.8 (15.8 to 33.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Moderate/severe chronic GvHD - number

| End point title | Moderate/severe chronic GvHD - number |
|---|---|

End point description:

Moderate or severe chronic graft versus host disease - number of patients with and without event

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

End point timeframe:

From 100 days after HSCT until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: subjects | | | | |
| With event | 12 | | | |
| Without event | 55 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Moderate/severe chronic GvHD - cumulative incidence

| End point title | Moderate/severe chronic GvHD - cumulative incidence |
|---|---|

End point description:

Moderate or severe chronic graft versus host disease - cumulative incidence

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

End point timeframe:

From 100 days after HSCT until 12 months after HSCT

| End point values | Full Analysis Set | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: percent | | | | |
| number (confidence interval 90%) | 18.8 (10.6 to 26.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Until 100 days after HSCT

Adverse event reporting additional description:

Adverse event reporting was based on the Safety Analysis Set. This includes all subjects enrolled in the trial who have received at least one dose of Treosulfan.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Treosulfan |

Reporting group description: -

| Serious adverse events | Treosulfan | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 70 (32.86%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | 1 | | |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Laryngeal hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary edema | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infections and infestations - Other, specify | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis viral | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| 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 / 70 (1.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Treosulfan | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 68 / 70 (97.14%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 21 / 70 (30.00%) | | |
| occurrences (all) | 33 | | |
| Hematoma | | | |
| subjects affected / exposed | 7 / 70 (10.00%) | | |
| occurrences (all) | 8 | | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Capillary leak syndrome | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Peripheral ischemia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 2 | | |
| Thromboembolic event | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders - Other, specify | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 51 / 70 (72.86%) | | |
| occurrences (all) | 96 | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 6 | | |
| Edema face | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | | |
| occurrences (all) | 6 | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | | |
| occurrences (all) | 6 | | |
| Chills | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 5 | | |
| Edema limbs | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Pain | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Localized edema | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 3 | | |
| Edema trunk | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Flu like symptoms | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 12 / 70 (17.14%) | | |
| occurrences (all) | 17 | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Testicular pain | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Uterine hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Vaginal hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 13 / 70 (18.57%) | | |
| occurrences (all) | 21 | | |
| Nasal congestion | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 7 / 70 (10.00%) | | | |
| occurrences (all) | 9 | | | |
| Dyspnea | | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | | | |
| occurrences (all) | 5 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | | |
| occurrences (all) | 4 | | | |
| Sore throat | | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | | |
| occurrences (all) | 6 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 3 | | | |
| Pulmonary edema | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Respiratory, thoracic and mediastinal disorders - Other, specify | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Sneezing | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Hiccups | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Laryngopharyngeal dysesthesia | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 2 | | | |
| Pharyngolaryngeal pain | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |

| | | | |
|---|---|---|---|
| Wheezing | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders - Other, specify | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 9 / 70 (12.86%) | | |
| occurrences (all) | 13 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 9 / 70 (12.86%) | | |
| occurrences (all) | 11 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 70 (11.43%) | | |
| occurrences (all) | 8 | | |
| Investigations - Other, specify | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 5 | | |
| Creatinine increased | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 5 | | |
| GGT increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 3 / 70 (4.29%)<br>3 | | |
| INR increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 70 (2.86%)<br>2 | | |
| Alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Fibrinogen decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Weight loss<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Injury, poisoning and procedural complications | | | |
| Bruising<br>subjects affected / exposed<br>occurrences (all) | 2 / 70 (2.86%)<br>2 | | |
| Fall<br>subjects affected / exposed<br>occurrences (all) | 2 / 70 (2.86%)<br>2 | | |
| Burn<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Postoperative hemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>2 | | |
| Vascular access complication<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>2 | | |
| Cardiac disorders | | | |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all) | 8 / 70 (11.43%)<br>9 | | |
| Sinus bradycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Heart failure | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 19 / 70 (27.14%) | | |
| occurrences (all) | 28 | | |
| Lethargy | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Tremor | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 7 | | |
| Dysesthesia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Paresthesia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Blood and lympatic disorders - Other, specify | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 3 | | |
| Hemolysis | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Thrombotic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Eye disorders | | | |
| Blurred vision | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Eye pain | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 5 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Eye disorders - Other, specify | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Optic nerve disorder | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Vitreous hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|---|---|---|---|
| Mucositis oral | | | | |
| subjects affected / exposed | 54 / 70 (77.14%) | | | |
| occurrences (all) | 57 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 48 / 70 (68.57%) | | | |
| occurrences (all) | 95 | | | |
| Diarrhea | | | | |
| subjects affected / exposed | 46 / 70 (65.71%) | | | |
| occurrences (all) | 69 | | | |
| Nausea | | | | |
| subjects affected / exposed | 32 / 70 (45.71%) | | | |
| occurrences (all) | 53 | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 22 / 70 (31.43%) | | | |
| occurrences (all) | 49 | | | |
| Constipation | | | | |
| subjects affected / exposed | 8 / 70 (11.43%) | | | |
| occurrences (all) | 10 | | | |
| Oral pain | | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | | | |
| occurrences (all) | 7 | | | |
| Dyspepsia | | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | | |
| occurrences (all) | 4 | | | |
| Anal pain | | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | | |
| occurrences (all) | 3 | | | |
| Dysphagia | | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | | |
| occurrences (all) | 3 | | | |
| Stomach pain | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Abdominal distension | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |

| | | | |
|---|---|---|---|
| Anal mucositis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Enterocolitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Esophageal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Esophagitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Gastritis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Oral hemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Pancreatitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Rectal mucositis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Rectal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Toothache<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Typhlitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Hepatobiliary disorders<br>Hepatobiliary disorders - Other, specify | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 25 / 70 (35.71%) | | |
| occurrences (all) | 29 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 20 / 70 (28.57%) | | |
| occurrences (all) | 29 | | |
| Pruritus | | | |
| subjects affected / exposed | 13 / 70 (18.57%) | | |
| occurrences (all) | 17 | | |
| Skin and subcutaneous tissue disorders - Other, specify | | | |
| subjects affected / exposed | 11 / 70 (15.71%) | | |
| occurrences (all) | 22 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 8 / 70 (11.43%) | | |
| occurrences (all) | 9 | | |
| Pain of skin | | | |
| subjects affected / exposed | 8 / 70 (11.43%) | | |
| occurrences (all) | 8 | | |
| Dry skin | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 4 | | |
| Erythroderma | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Periorbital edema | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 3 | | |
| Rash acneiform | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 3 | | |
| Skin ulceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 2 / 70 (2.86%)<br>2 | | |
| Urticaria<br>subjects affected / exposed<br>occurrences (all) | 2 / 70 (2.86%)<br>3 | | |
| Alopecia<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Bullous dermatitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Palmar-plantar erythrodysesthesia syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Renal and urinary disorders | | | |
| Hematuria<br>subjects affected / exposed<br>occurrences (all) | 4 / 70 (5.71%)<br>5 | | |
| Urinary tract pain<br>subjects affected / exposed<br>occurrences (all) | 4 / 70 (5.71%)<br>4 | | |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all) | 3 / 70 (4.29%)<br>3 | | |
| Bladder spasm<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Cystitis noninfective<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Renal and urinary disorders - Other, specify<br>subjects affected / exposed<br>occurrences (all) | 1 / 70 (1.43%)<br>1 | | |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 13 / 70 (18.57%) | | |
| occurrences (all) | 19 | | |
| Bone pain | | | |
| subjects affected / exposed | 7 / 70 (10.00%) | | |
| occurrences (all) | 7 | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 6 | | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Chest wall pain | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Infections and infestations - Other, specify | | | |
| subjects affected / exposed | 43 / 70 (61.43%) | | |
| occurrences (all) | 113 | | |
| Catheter related infection | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 6 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | | |
| occurrences (all) | 6 | | |
| Bladder infection | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 70 (4.29%) | | | |
| occurrences (all) | 3 | | | |
| Bronchial infection | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Enterocolitis infectious | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Mucosal infection | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Skin infection | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 4 | | | |
| Upper respiratory infection | | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | | |
| occurrences (all) | 2 | | | |
| Conjunctivitis infective | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Laryngitis | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Nail infection | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Papulopustular rash | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 2 | | | |
| Penile infection | | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | | |
| occurrences (all) | 1 | | | |
| Rhinitis infective | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalemia | | | |
| subjects affected / exposed | 11 / 70 (15.71%) | | |
| occurrences (all) | 11 | | |
| Hypomagnesemia | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 6 | | |
| Iron overload | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Glucose intolerance | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Alkalosis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Anorexia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 June 2014 | Relevant changes were:<br>• Modification of treatment Regimen B<br>• The schedule of assessments was revised<br>• The reference for the grading of GvHD and cGvHD was adapted. |
| 28 July 2015 | Relevant changes were:<br>• Specification inclusion and exclusion criteria<br>• Specification on SAE/SAR reporting and time frame of reporting pregnancies<br>• Specification on conditioning treatment<br>• Specifications for secondary endpoints and PK sampling<br>• Specification on documentation of concomitant medication<br>• Specification on statistical data analysis |
| 25 April 2016 | Relevant changes were:<br>• Specification on reference safety information<br>• Specification on PK sampling<br>• Revision of patient information documents |
| 20 February 2017 | • CRO change was implemented<br>• Clarification on a secondary endpoint<br>• Deletion on country-specific information |

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 |

Notes: