



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) | EMA-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 | | | |
| 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 | | | |
| Units: years | | | |
| median | 9.5 | | |
| full range (min-max) | 0 to 17 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 44 | 44 | |
| Disease | | | |
| 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 | | | |
| Units: Subjects | | | |
| First | 65 | 65 | |
| Second | 5 | 5 | |
| Donor type | | | |
| Units: Subjects | | | |
| MSD - matched sibling donor | 13 | 13 | |
| MFD - matched family donor | 1 | 1 | |
| MUD - matched unrelated donor | 56 | 56 | |
| BSA - Body surface area | | | |
| Units: m ² | | | |
| 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 occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Delirium subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Depression subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Psychiatric disorders - Other, specify subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 9 / 70 (12.86%) 13 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 9 / 70 (12.86%) 11 | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 8 / 70 (11.43%) 8 | | |
| Investigations - Other, specify subjects affected / exposed occurrences (all) | 4 / 70 (5.71%) 5 | | |
| Creatinine increased subjects affected / exposed occurrences (all) | 3 / 70 (4.29%) 5 | | |
| GGT increased | | | |

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

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 70 (2.86%) 3 | | |
| Hemolysis subjects affected / exposed occurrences (all) | 2 / 70 (2.86%) 2 | | |
| Thrombotic thrombocytopenic purpura subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 2 / 70 (2.86%) 2 | | |
| Eye disorders Blurred vision subjects affected / exposed occurrences (all) | 4 / 70 (5.71%) 4 | | |
| Eye pain subjects affected / exposed occurrences (all) | 4 / 70 (5.71%) 5 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 70 (4.29%) 3 | | |
| Eye disorders - Other, specify subjects affected / exposed occurrences (all) | 2 / 70 (2.86%) 2 | | |
| Dry eye subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Optic nerve disorder subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Vitreous hemorrhage subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 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 | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Esophageal pain | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Esophagitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Oral hemorrhage | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Rectal mucositis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Rectal pain | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Typhlitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Hepatobiliary disorders | | | |
| 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 | 2 / 70 (2.86%) | | |
| occurrences (all) | 2 | | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | | |
| occurrences (all) | 3 | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Bullous dermatitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Hematuria | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 5 | | |
| Urinary tract pain | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | | |
| occurrences (all) | 4 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | | |
| occurrences (all) | 3 | | |
| Bladder spasm | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders - Other, specify | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |

| | | | |
|--|-------------------------|--|--|
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 13 / 70 (18.57%) 19 | | |
| Bone pain subjects affected / exposed occurrences (all) | 7 / 70 (10.00%) 7 | | |
| Back pain subjects affected / exposed occurrences (all) | 6 / 70 (8.57%) 6 | | |
| Myalgia subjects affected / exposed occurrences (all) | 3 / 70 (4.29%) 3 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Arthritis subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Chest wall pain subjects affected / exposed occurrences (all) | 1 / 70 (1.43%) 1 | | |
| Infections and infestations | | | |
| Infections and infestations - Other, specify subjects affected / exposed occurrences (all) | 43 / 70 (61.43%) 113 | | |
| Catheter related infection subjects affected / exposed occurrences (all) | 6 / 70 (8.57%) 6 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 70 (8.57%) 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: <ul style="list-style-type: none">• Modification of treatment Regimen B• The schedule of assessments was revised• The reference for the grading of GvHD and cGvHD was adapted. |
| 28 July 2015 | Relevant changes were: <ul style="list-style-type: none">• Specification inclusion and exclusion criteria• Specification on SAE/SAR reporting and time frame of reporting pregnancies• Specification on conditioning treatment• Specifications for secondary endpoints and PK sampling• Specification on documentation of concomitant medication• Specification on statistical data analysis |
| 25 April 2016 | Relevant changes were: <ul style="list-style-type: none">• Specification on reference safety information• Specification on PK sampling• Revision of patient information documents |
| 20 February 2017 | <ul style="list-style-type: none">• CRO change was implemented• Clarification on a secondary endpoint• 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: