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	30 September 2019

Results information

Result version number	v2 (current)
This version publication date	16 May 2020
First version publication date	02 May 2018
Version creation reason	• New data added to full data set Study results were analyzed for the primary endpoint 12 month after the last trial subject completed the 12 months follow up visit and posted in May 2018. Meanwhile the long term 3-year follow up period of the trial was completed in Sep 2019 and therefore results will updated or added.

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	Final
Date of interim/final analysis	02 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	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
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
Death	7

Period 2

Period 2 title	Longer-term follow-up period
Is this the baseline period?	No
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 2	Treosulfan
Started	63
Completed	56
Not completed	7
Consent withdrawn by subject	1
Death	5
Lost to follow-up	1

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: 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: -	
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 Transplant (Treatment)-related Mortality - number

End point title	Freedom from Transplant (Treatment)-related Mortality - number[1]
End point description:	
Freedom from Transplant (Treatment)-related Mortality until day +100 after HSCT - number of subjects with and without event The primary endpoint, freedom from transplant (treatment)-related mortality, was defined as death from any transplant-related cause from the day of first administration of trial medication (ie visit Day -6) until 100 days after HSCT.	
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 with event				
Without event	69			
With event	1			

Statistical analyses

No statistical analyses for this end point

Primary: Freedom from Transplant (Treatment)-related Mortality - rate

End point title	Freedom from Transplant (Treatment)-related Mortality - rate[2]

End point description:

Freedom from Transplant (Treatment)-related Mortality until day +100 after HSCT - percentage of subjects without transplant (treatment) - related death.
The primary endpoint, freedom from transplant (treatment)-related mortality, was defined as death from any transplant-related cause from the day of first administration of trial medication (ie visit Day -6) until 100 days after HSCT.

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.
Time to engraftment was defined as the time span between end of HSCT and neutrophil engraftment. The date of reaching engraftment was the documented “date of engraftment”. Death from any cause, relapse/progression or use of rescue therapies until the date of primary graft failure or documentation of engraftment status (whatever occurred first) were competing events.
The maximum conditional cumulative incidence is reported here.

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.
Time to engraftment was defined as the time span between end of HSCT and neutrophil engraftment. The date of reaching engraftment was the documented "date of engraftment". Death from any cause, relapse/progression or use of rescue therapies until the date of primary graft failure or documentation of engraftment status (whatever occurred first) were competing events.
The maximum conditional cumulative incidence is reported here.

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 at visit Day 28 - number

End point title	Incidence of complete donor type chimerism at visit Day 28 - number

End point description:

Incidence of complete donor type chimerism at visit Day +28.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 visit Day +28 - rate

End point title	Incidence of complete donor type chimerism visit Day +28 - rate

End point description:

Incidence of complete donor type chimerism at visit Day +28.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 visit Day +100 - number

End point title	Incidence of complete donor type chimerism visit Day +100 - number

End point description:

Incidence of complete donor type chimerism at visit Day +100.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a

value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 at visit Day +100 - rate

End point title	Incidence of complete donor type chimerism at visit Day +100 - rate

End point description:

Incidence of complete donor type chimerism at visit Day +100.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 at visit Month 12 - number

End point title	Incidence of complete donor type chimerism at visit Month 12 - number

End point description:

Incidence of complete donor type chimerism at visit Month 12.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 at visit Month 12 - rate

End point title	Incidence of complete donor type chimerism at visit Month 12 - rate

End point description:

Incidence of complete donor type chimerism at visit Month 12.
Based on the examinations (documented on the CRF), complete donor-type chimerism was defined if a value of >= 95% is detected. The incidences of complete donor-type chimerism were estimated as the number of subjects with complete chimerism divided by the total number of subjects at risk.

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 (cumulative)

End point title	Non-relapse mortality - number (cumulative)

End point description:

Non-relapse mortality (NRM) was defined as the probability of dying in the absence of persisting disease or previous occurrence of relapse/progression or graft failure. The associated time span was defined as the interval from end of HSCT to death from all causes without previous graft failure or relapse/progression of the underlying disease. Relapse/progression and graft failure were considered competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Subjects with event - month 12	1			
Subjects with event - month 24	2			
Subjects with event - month 36	2			

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:

Non-relapse mortality (NRM) was defined as the probability of dying in the absence of persisting disease or previous occurrence of relapse/progression or graft failure. The associated time span was defined as the interval from end of HSCT to death from all causes without previous graft failure or relapse/progression of the underlying disease. Relapse/progression and graft failure were considered competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	1.4 (0.0 to 3.8)			
Month 24	2.9 (0.0 to 6.1)			
Month 36	2.9 (0.0 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Primary graft failure - number

End point title	Primary graft failure - number

End point description:

The rate of primary graft failure was estimated as the number of subjects with primary graft failure divided by the total number of subjects receiving HSCT within the 12-months trial period.
In the case that graft failure was ticked as "unknown" on the CRF and a relapse / progression was documented, the appropriate subject was not considered a graft failure but a disease relapse / progression.

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:

The rate of primary graft failure was estimated as the number of subjects with primary graft failure divided by the total number of subjects receiving HSCT within the 12-months trial period.
In the case that graft failure was ticked as "unknown" on the CRF and a relapse / progression was documented, the appropriate subject was not considered a graft failure but a disease relapse / progression.

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:

The rate of secondary graft failure was estimated as the number of subjects with secondary graft failure divided by the total number of subjects who have engrafted after stem cell transplantation (ie alive without documented primary graft failure) within the 12-months trial period.
In the case that graft failure was ticked as "unknown" on the CRF and a relapse / progression was documented, the appropriate subject was not considered a graft failure but a disease relapse / progression.

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:

The rate of secondary graft failure was estimated as the number of subjects with secondary graft failure divided by the total number of subjects who have engrafted after stem cell transplantation (ie alive without documented primary graft failure) within the 12-months trial period.
In the case that graft failure was ticked as "unknown" on the CRF and a relapse / progression was documented, the appropriate subject was not considered a graft failure but a disease relapse / progression.

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 (cumulative)

End point title	Incidence of relapse/progression - number (cumulative)

End point description:

The incidence of relapse/progression (RI) was defined as the probability of having a relapse/progression of the underlying disease. Deaths without relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Subjects with event - month 12	11			
Subjects with event - month 24	16			
Subjects with event - month 36	16			

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:

The incidence of relapse/progression (RI) was defined as the probability of having a relapse/progression of the underlying disease. Deaths without relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	15.7 (8.6 to 22.9)			
Month 24	23.0 (14.7 to 31.3)			
Month 36	23.0 (14.7 to 31.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse/progression-free survival - number (cumulative)

End point title	Relapse/progression-free survival - number (cumulative)

End point description:

Relapse-free/progression-free survival was defined as the time length between end of HSCT and the date of relapse/progression of the underlying disease or death due to any cause.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Events - month 12	12			
Events - month 24	19			

Events - month 36	19			

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:

Relapse-free/progression-free survival was defined as the time length between end of HSCT and the date of relapse/progression of the underlying disease or death due to any cause.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	82.9 (73.9 to 89.0)			
Month 24	72.7 (62.7 to 80.4)			
Month 36	72.7 (62.7 to 80.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival - number (cumulative)

End point title	Overall survival - number (cumulative)

End point description:

Overall survival (OS) after HSCT was defined as the probability of surviving. Survival time was defined as the time period between end of HSCT and the date of death due to any cause.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Death - month 12	6			
Death - month 24	10			
Death - month 36	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival - rate

End point title	Overall survival - rate

End point description:

Overall survival (OS) after HSCT was defined as the probability of surviving. Survival time was defined as the time period between end of HSCT and the date of death due to any cause.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	91.4 (83.9 to 95.5)			
Month 24	85.7 (77.1 to 91.2)			
Month 36	84.3 (75.5 to 90.1)			

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
Time to acute GvHD (aGvHD) was defined as the time between end of HSCT and the date of first occurrence of acute GvHD. Death, relapse/progression and graft failure within 100 days after end of HSCT were competing events.

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
Time to acute GvHD (aGvHD) was defined as the time between end of HSCT and the date of first occurrence of acute GvHD. Death, relapse/progression and graft failure within 100 days after end of HSCT were competing events.

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.
Time to acute GvHD (aGvHD) was defined as the time between end of HSCT and the date of first occurrence of acute GvHD. Death, relapse/progression and graft failure within 100 days after end of HSCT were competing events.

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.
Time to acute GvHD (aGvHD) was defined as the time between end of HSCT and the date of first occurrence of acute GvHD. Death, relapse/progression and graft failure within 100 days after end of HSCT were competing events.

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: Overall chronic GvHD - number (cumulative)

End point title	Overall chronic GvHD - number (cumulative)

End point description:

Chronic graft versus host disease - number.
Subjects are at risk (evaluable) for chronic GvHD (cGvHD) if they have survived 100 days after end of HSCT relapse/progression-free and graft-failure-free. In addition, subjects with premature trial termination at Day +100 visit are excluded from the risk set. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD. Death, relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Events - month 12	16			
Events - month 24	17			
Events - month 36	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall chronic GvHD - cumulative incidence

End point title	Overall chronic GvHD - cumulative incidence

End point description:

Chronic graft versus host disease - cumulative incidence
Subjects are at risk (evaluable) for chronic GvHD (cGvHD) if they have survived 100 days after end of HSCT relapse/progression-free and graft-failure-free. In addition, subjects with premature trial termination at Day +100 visit are excluded from the risk set. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD. Death, relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	23.9 (15.3 to 32.4)			
Month 24	25.4 (16.6 to 34.1)			
Month 36	25.4 (16.6 to 34.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Moderate/severe chronic GvHD - number (cumulative)

End point title	Moderate/severe chronic GvHD - number (cumulative)

End point description:

Moderate or severe chronic graft versus host disease - number of patients with and without Event. Subjects are at risk (evaluable) for chronic GvHD (cGvHD) if they have survived 100 days after end of HSCT relapse/progression-free and graft-failure-free. In addition, subjects with premature trial termination at Day +100 visit are excluded from the risk set. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD. Death, relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: subjects				
Events - month 12	12			
Events - month 24	13			
Events - month 36	13			

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.

Subjects are at risk (evaluable) for chronic GvHD (cGvHD) if they have survived 100 days after end of HSCT relapse/progression-free and graft-failure-free. In addition, subjects with premature trial termination at Day +100 visit are excluded from the risk set. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD. Death, relapse/progression and graft failure are competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 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%)				
Month 12	17.9 (10.2 to 25.6)			
Month 24	19.4 (11.5 to 27.4)			
Month 36	19.4 (11.5 to 27.4)			

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

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	8 / 70 (11.43%)		
occurrences (all)	12		
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	3 / 70 (4.29%)		
occurrences (all)	3		
INR increased			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Alkaline phosphatase increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Fibrinogen decreased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Burn			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Postoperative hemorrhage			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	2		
Vascular access complication			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	2		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	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			
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 occurrences (all)	2 / 70 (2.86%) 2		
Urticaria subjects affected / exposed occurrences (all)	2 / 70 (2.86%) 3		
Alopecia subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1		
Bullous dermatitis subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1		
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1		
Renal and urinary disorders Hematuria subjects affected / exposed occurrences (all)	4 / 70 (5.71%) 5		
Urinary tract pain subjects affected / exposed occurrences (all)	4 / 70 (5.71%) 4		
Acute kidney injury subjects affected / exposed occurrences (all)	3 / 70 (4.29%) 3		
Bladder spasm subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1		
Cystitis noninfective subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 1		
Renal and urinary disorders - Other, specify subjects affected / exposed occurrences (all)	1 / 70 (1.43%) 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: • 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: • 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: • Specification on reference safety information • Specification on PK sampling • Revision of patient information documents
20 February 2017	• 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: