



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
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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
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Treosulfan
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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			

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

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: