Clinical trial results:
Clinical phase III trial to compare Treosulfan-based conditioning therapy with Busulfan-based reduced-intensity conditioning (RIC) prior to allogeneic haematopoietic stem cell transplantation in patients with AML or MDS considered ineligible to standard conditioning regimens

Summary

EudraCT number	2008-002356-18
Trial protocol	DE IT PL FI FR HU
Global end of trial date	25 January 2018

Results information

Result version number	v1 (current)
This version publication date	30 January 2019
First version publication date	30 January 2019
Summary attachment (see zip file)	2008-002356-18_MC-FludT.14-L_Redacted Synopsis_Part I (2008-002356-18_MC-FludT.14-L_Redacted Synopsis_Part I.pdf)

Trial information

Trial identification

Sponsor protocol code	MC-FludT.14/L

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00822393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	medac Gesellschaft fuer klinische Spezialpraeparate 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2018
Global end of trial reached?	Yes
Global end of trial date	25 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomised controlled clinical trial was designed to show at least non-inferiority of treosulfan-based conditioning to reduced-intensity conditioning therapy based on intravenous (i.v.) busulfan and to compare the associated safety profiles. The aim of the study was to compare event-free survival within 2 years after the allogeneic haematopoietic stem cell transplantation (HSCT) between treosulfan-based conditioning and busulfan-based conditioning. Events are defined as relapse of desease, graft failure or death (whatever occurs first).

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.
In addition, a Data Monitoring Committee (DMC) was implemented to periodically assess the safety and efficacy as pre-specified in the clinical trial protocol. The DMC monitored the accumulating data from the clinical trial to detect and report early evidence of pre-specified or unanticipated benefit or harm to trial participants that was attributable to one of the treatments under evaluation.
The patients were informed about the modalities of the clinical study by an authorized member of the study team (physician) in a language they understood.
Patients could withdraw from the study without giving reasons and without penalty or loss of benefits to which the patient was otherwise entitled.

Background therapy:

Mandatory immunosuppression and GvHD-Prophylaxis were given in the test and reference arm. This included Fludarabine, Ciclosporin, Methotrexate, Ca-Folinate for all countries involved.
In addition patients in Germany, Italy, Hungary, Poland received ATG-S-Fresenius / Grafalon®, and in France ATG-Thymoglobuline (in case of matched unrelated donor (MUD) only).
Other concomitant treatments, which were not standardized, were conducted according to the center-specific policy.

Evidence for comparator:

Busilvex® (i.v. busulfan) was selected as reference regimen within this trial. This reference treatment regimen was confirmed by EMA.
The drug is registered in Europe for conditioning treatment prior to conventional haematopoietic progenitor cell Transplantation.
The combination of dose-reduced busulfan and fludarabine is approved and actually one of the most frequently used and widely accepted regimens. Especially for leukaemia, lymphoma or MDS patients RIC (reduced intensity conditioning treatment) with dose-reduced busulfan was extensively evaluated within retrospective and prospective clinical trials.

Actual start date of recruitment	13 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 77
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 387
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 57
Worldwide total number of subjects	570
EEA total number of subjects	570

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	422
From 65 to 84 years	148
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was registered on 21-04-2008 with FSI on 24-11-2008. Following the recommendation of the DMC (20-02-2012), the trial was temporarily suspended and newly set up after amendment 03 with significant design changes. Recruitment re-started on 13-06-2013. Results provided are based exclusively on the 570 patients randomized after 13-06-2013.

Pre-assignment

Screening details:

A total of 570 subjects were enrolled at 31 sites in 5 countries. 553 subjects received IMP (test or reference medication).
17 subjects dropped out before treatment: 16 subjects did not meet the inclusion and exclusion criteria and 1 subject withdrew consent.

Period 1

Period 1 title	Treatment and 24 month follow up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The sponsor was blinded with respect to aggregated data until data extraction for the second interim analysis (final confirmatory analysis).

Arms

Are arms mutually exclusive?	Yes
Arm title	Treosulfan

Arm description:

The Treosulfan arm includes all randomised patients who were treated with Treosulfan at least once.

Arm type	Experimental
Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan 10 g/m² body surface area (BSA), 2 hours i.v. infusion Day -4, -3, -2
The 2-hour infusion of the total Treosulfan solution was to be given prior to fludarabine infusion (in case both drugs were given on the same day).

Arm title	Busulfan

Arm description:

The Busulfan arm includes all randomised patients who were treated with Busulfan at least once.

Arm type	Active comparator
Investigational medicinal product name	i.v. Busulfan
Investigational medicinal product code	
Other name	Busilvex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan 4 x 0.8 mg/kg Body weight, 2 hours i.v. infusion every 6 hours, Day -4, -3 (total of eight doses).

Number of subjects in period 1[1]	Treosulfan	Busulfan
Started	270	283
Completed	191	165
Not completed	79	118
Adverse event, serious fatal	8	6
Consent withdrawn by subject	2	2
Did not receive transplant	2	-
Death	64	101
AML progression	1	-
Lost to follow-up	-	7
Site closure	2	2

Notes:

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

Period 2

Period 2 title	Post-surveillance evaluation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Post-surveillance_Treosulfan

Arm description:

This arm of the post surveillance period includes all patients who received Treosulfan and completed the study alive 2 years after HSCT.
Post-surveillance was conducted one year after transplantation of the last randomised patient. Follow-up data were obtained for a period of up to 4 years after transplantation.
A post surveillance visit was not applicable for 10 patients because the post surveillance visit would have to be performed shortly after the 24 Month visit.
For 1 patient the post-surveillance visit was filled in although the Month 24 visit was not performed.

Arm type	Experimental
Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan 10 g/m², 2 hours i.v. infusion Day -4, -3, -2
A 2-hour infusion of the total Treosulfan solution was to be given prior to fludarabine Infusion (in case both drugs were given on the same day).

Arm title	Post-surveillance_Busulfan

Arm description:

This arm of the post surveillance period includes all patients who received Busulfan and completed the study alive 2 years after HSCT.
Post-surveillance was conducted one year after transplantation of the last randomised patient. Follow-up data were obtained for a period of up to 4 years after transplantation.
A post surveillance visit was not applicable for 10 patients because the post surveillance visit would have to be performed shortly after the 24 Month visit.
For 1 patient the post-surveillance visit was filled in although the Month 24 visit was not performed.

Arm type	Active comparator
Investigational medicinal product name	i.v. Busulfan
Investigational medicinal product code	
Other name	Busilvex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Busulfan 4 x 0.8 mg/kg Body weight, 2 hours i.v. infusion every 6 hours, Day -4, -3 (total of eight doses).

Number of subjects in period 2[2]	Post-surveillance_Treosulfan	Post-surveillance_Busulfan
Started	135	117
Completed	116	101
Not completed	19	16
Death	9	5
Lost to follow-up	-	1
Not applicable	10	10

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only subjects who had completed the Month 24 visit were qualified for the "Post-surveillance evaluation" period.

Baseline characteristics

Reporting groups	
Reporting group title	Treosulfan
Reporting group description:	
The Treosulfan arm includes all randomised patients who were treated with Treosulfan at least once.	
Reporting group title	Busulfan
Reporting group description:	
The Busulfan arm includes all randomised patients who were treated with Busulfan at least once.	

Reporting group values	Treosulfan	Busulfan	Total
Number of subjects	270	283	553
Age categorical Units: Subjects			
Adults (18-64 years)	197	215	412
From 65-84 years	73	68	141
Age continuous Units: years			
arithmetic mean	59.3	59.9	
standard deviation	± 6.5	± 6.0	-
Gender categorical Units: Subjects			
Female	107	110	217
Male	163	173	336
Risk group			
The number of patients randomized has been stratified by cytogenetic and/or molecular risk group for acute myeloid leukaemia (AML) and revised international prognostic scoring system (IPSS-R) for myelodysplastic Syndrome (MDS). Risk group I: low risk and intermediate risk for AML or very low/low/intermediate IPSS-R for MDS Risk group II: high risk for AML and high/very high IPSS-R risk for MDS			
Units: Subjects			
Risk group I	127	149	276
Risk group II	143	134	277
Donor type			
The number of patients randomized has been stratified by the availability of a human leukocyte antigen (HLA)-identical sibling donor (MRD) or HLA-identical unrelated donor (MUD).			
Units: Subjects			
MRD	63	68	131
MUD	207	215	422
Disease Units: Subjects			
AML	185	168	353
MDS	85	115	200

End points

End points reporting groups

Reporting group title	Treosulfan

Reporting group description:

The Treosulfan arm includes all randomised patients who were treated with Treosulfan at least once.

Reporting group title	Busulfan

Reporting group description:

The Busulfan arm includes all randomised patients who were treated with Busulfan at least once.

Reporting group title	Post-surveillance_Treosulfan

Reporting group description:

This arm of the post surveillance period includes all patients who received Treosulfan and completed the study alive 2 years after HSCT.
Post-surveillance was conducted one year after transplantation of the last randomised patient. Follow-up data were obtained for a period of up to 4 years after transplantation.
A post surveillance visit was not applicable for 10 patients because the post surveillance visit would have to be performed shortly after the 24 Month visit.
For 1 patient the post-surveillance visit was filled in although the Month 24 visit was not performed.

Reporting group title	Post-surveillance_Busulfan

Reporting group description:

This arm of the post surveillance period includes all patients who received Busulfan and completed the study alive 2 years after HSCT.
Post-surveillance was conducted one year after transplantation of the last randomised patient. Follow-up data were obtained for a period of up to 4 years after transplantation.
A post surveillance visit was not applicable for 10 patients because the post surveillance visit would have to be performed shortly after the 24 Month visit.
For 1 patient the post-surveillance visit was filled in although the Month 24 visit was not performed.

Subject analysis set title	Treosulfan_ Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Treosulfan Full Analysis Set (FAS) includes all randomised patients who were treated with Treosulfan at least once and had at least one efficacy parameter documented after baseline. The patients within the FAS were analysed in their initial group of randomisation (intention to treat principle).

Subject analysis set title	Busulfan_ Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Busulfan Full Analysis Set (FAS) includes all randomised patients who were treated with Busulfan at least once and had at least one efficacy parameter documented after baseline. The patients within the FAS were analysed in their initial group of randomisation (intention to treat principle).

Primary: Event-free survival (EFS) within 2 years

End point title	Event-free survival (EFS) within 2 years

End point description:

Event-free survival (EFS) within 2 years after transplantation measured from time of start of HSCT (= day 0) to time of event based on Kaplan-Meier estimates.
Events are defined as relapse of disease, graft failure or death (whatever occurs first).

End point type	Primary

End point timeframe:

From day 0 (start of HSCT) to time to event within 2 years.

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	65.7 (59.5 to 71.2)	51.2 (45.0 to 57.0)		

Statistical analyses

Statistical analysis title	Hazard Ratio Treosulfan/Busulfan

Statistical analysis description:

The statistical analysis shows the p-value for non-inferiority with respect to event free survival including the post surveillance evaluation. The non-inferiority margin for the hazard ratio is 1.3.

Comparison groups	Treosulfan_ Full Analysis Set v Busulfan_ Full Analysis Set
Number of subjects included in analysis	551
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.000001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.84

Secondary: Incidence of CTC grade III/IV mucositis

End point title	Incidence of CTC grade III/IV mucositis

End point description:

Comparative evaluation of incidence of CTC grade III/IV mucositis at any location (i.e. one of the CTCAE version 4.03 terms anal mucositis, mucositis oral, rectal mucositis, small intestinal mucositis, laryngeal mucositis, pharyngeal mucositis, tracheal mucositis).

End point type	Secondary

End point timeframe:

day -4 to day +28
Day -4 was chosen as starting point for evaluation since administration of the investigational product started on this day.

End point values	Treosulfan	Busulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	283		
Units: Percentage of participants				
number (confidence interval 95%)	5.9 (3.4 to 9.4)	7.4 (4.7 to 11.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Comparative evaluation of overall survival

End point title	Comparative evaluation of overall survival

End point description:

Iincidence of overall survival based on Kaplan-Meier estimates.
Overall survival is defined as the probability of survival irrespective of disease status at any point in time within 2 years after HSCT.

End point type	Secondary

End point timeframe:

Within 2 years after HSCT

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	72.7 (66.8 to 77.8)	60.2 (54.0 to 65.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of relapse/progression

End point title	Cumulative incidence of relapse/progression

End point description:

Relapse/progression incidence is defined as the probability of having a relapse/progression within 2 years of HSCT.
Death and graft failure are considered as competing events.

End point type	Secondary

End point timeframe:

Within 2 years after HSCT

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	22.0 (16.9 to 27.1)	25.2 (20.0 to 30.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of non-relapse mortality

End point title	Cumulative incidence of non-relapse mortality

End point description:

Non-relapse mortality is defined as the probability of dying without occurrence of a relapse/progression. The associated time span is defined as the interval from day 0 to death without previous relapse/progression within the 24-month study period. Relapse/progression and graft failure are considered as competing events.

End point type	Secondary

End point timeframe:

Within 2 years after HSCT

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	12.0 (8.0 to 15.9)	20.4 (15.5 to 25.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of transplantation-related mortality

End point title	Incidence of transplantation-related mortality

End point description:

Incidence of transplantation-related mortality based on Kaplan-Meier estimates.
Transplantation-related mortality is defined as all deaths occurring due to GvHD, cardiac toxicity, pulmonary toxicity, interstitial pneumonitis, haemorrhage, hepatic sinusoidal obstruction syndrome

(HSOS), skin toxicity, Epstein-Barr virus (EBV) proliferative disease, renal failure, gastrointestinal toxicity, rejection/poor graft function, CNS toxicity, multiple organ failure, infections (bacterial, viral, fungal, parasitic, unknown), or other HSCT-related causes.

End point type	Secondary

End point timeframe:

Within 2 years after HSCT

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	12.8 (9.2 to 17.7)	24.1 (19.1 to 30.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Conditional cumulative incidence of engraftment: Reconstitution of granulopoiesis

End point title	Conditional cumulative incidence of engraftment: Reconstitution of granulopoiesis

End point description:

Time to engraftment is defined as the time span between day 0 and neutrophil engraftment. Reconstitution of granulopoiesis was documented by specifying the first of 3 consecutive days with absolute neutrophilic granulocyte count > 0.5 x 10^9/L in the peripheral blood.

End point type	Secondary

End point timeframe:

day +28

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	96.2 (93.4 to 99.1)	96.8 (94.6 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Conditional cumulative incidence of engraftment: Reconstitution of leukopoiesis

End point title	Conditional cumulative incidence of engraftment: Reconstitution of leukopoiesis

End point description:

Time to engraftment is defined as the time span between day 0 and leukocyte engraftment. Reconstitution of leukopoiesis was documented by specifying the first of 3 consecutive days with total WBC count > 1 x 10^9/L in the peripheral blood.

End point type	Secondary

End point timeframe:

day +28

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	98.5 (96.1 to 100)	97.2 (95.2 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Conditional cumulative incidence of engraftment: Reconstitution of thrombopoiesis

End point title	Conditional cumulative incidence of engraftment: Reconstitution of thrombopoiesis

End point description:

Time to engraftment is defined as the time span between day 0 and platelet engraftment. Reconstitution of thrombopoiesis was documented by specifying the first of 3 consecutive days with platelets > 20 x 10^9/L in the absence of platelet transfusion.

End point type	Secondary

End point timeframe:

day +28

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	94.7 (92.0 to 97.4)	97.8 (96.3 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete donor-type chimerism Day +28

End point title	Complete donor-type chimerism Day +28

End point description:

Comparative evaluation of day +28 incidence of complete donor-type chimerism.
Complete donor-type chimerism is defined by a donor to patient ratio of >= 95%.
The Day +28 incidence of complete donor type chimerism had been estimated as the number of patients with complete chimerism divided by the total number of patients at risk. Patients are at risk for statistical analysis of chimerism at Day +28 if they have an examination at the Day +28 visit or they have survived day +29.

End point type	Secondary

End point timeframe:

day +28

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	263	282		
Units: percent				
number (confidence interval 95%)	93.2 (89.4 to 95.9)	83.3 (78.5 to 87.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete donor-type chimerism Day +100

End point title	Complete donor-type chimerism Day +100

End point description:

Comparative evaluation of day +100 incidence of complete donor-type chimerism.
Complete donor-type chimerism is defined by a donor to patient ratio of >= 95%.
The Day +100 incidence of complete donor type chimerism had been estimated as the number of patients with complete chimerism divided by the total number of patients at risk. Patients are at risk for statistical analysis of chimerism at Day +100 if they have an examination at the Day +100 visit or they have survived day +107.

End point type	Secondary

End point timeframe:

day +100

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	252	263		
Units: percent				
arithmetic mean (confidence interval 95%)	86.1 (81.2 to 90.1)	80.2 (74.9 to 84.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Acute GvHD (Grade I-IV on day +100)

End point title	Acute GvHD (Grade I-IV on day +100)

End point description:

Comparative evaluation of cumulative incidence of acute GvHD Grade I-IV.
Time to acute GvHD (aGvHD) is defined as the time between day 0 and the date of first occurrence of acute GvHD.

End point type	Secondary

End point timeframe:

day +100

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	283		
Units: percent				
number (confidence interval 95%)	52.8 (46.8 to 58.8)	57.2 (51.5 to 63.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic GvHD

End point title	Chronic GvHD

End point description:

Comparative evaluation of cumulative incidence of chronic GvHD.
Patients are at risk (evaluable) for chronic GvHD (cGvHD) if they have survived 100 days after end of HSCT relapse-free and graft-failure-free.

End point type	Secondary

End point timeframe:

Day +100 until 2 years after transplantation

End point values	Treosulfan_ Full Analysis Set	Busulfan_ Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	232		
Units: percent				
number (confidence interval 95%)	61.7 (55.1 to 68.3)	60.3 (53.8 to 66.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other CTC grade III/IV adverse events

End point title	Other CTC grade III/IV adverse events

End point description:

Comparative evaluation of incidence of other significant CTC grade III/IV adverse events.
Other significant adverse events in this trial (beside of mucositis) are HSOS (hepatic sinusoidal obstruction syndrome) (reported terms “HSOS”, “HSOS (VOD" (veno-occlusive disease)) etc. as determined by medical expert; allocated to CTCAE term “hepatobiliary disorders – other, specify”), seizures (CTCAE term “seizure”), and blood bilirubin increased (CTCAE term “blood bilirubin increased”) between day -4 and day +28.

End point type	Secondary

End point timeframe:

Day -4 to Day +28
Day -4 was chosen as starting point for evaluation since administration of the investigational product started on this day.

End point values	Treosulfan	Busulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	283		
Units: percent				
number (confidence interval 95%)				
HSOS	0.0 (0.0 to 1.4)	0.4 (0.0 to 2.0)		
Seizures	0.4 (0.0 to 2.0)	0.0 (0.0 to 1.3)		
Blood bilirubin increased	3.3 (1.5 to 6.2)	2.8 (1.2 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse event from day -4 to day +28 (related to the allogeneic haematopoietic stem cell transplantation).

Adverse event reporting additional description:

Adverse event reporting is based on the Safety Analysis Set (SAS). The SAS consists of all randomized patients who were treated at least one time with study medication.
Patients reporting more than one episode of the same event were counted only once by the worst CTCAE Grade.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Treosulfan_ Safety Analysis Set

Reporting group description:

The Treosulfan Safety Analysis Set (SAS) includes all randomised patients who were treated with Treosulfan at least once. All patients were analysed within their group of actual treatment.

Reporting group title	Busulfan_ Safety Analysis Set

Reporting group description:

The Busulfan Safety Analysis Set (SAS) includes all randomised patients who were treated with Busulfan at least once. All patients were analysed within their group of actual treatment.

Serious adverse events	Treosulfan_ Safety Analysis Set	Busulfan_ Safety Analysis Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 270 (8.52%)	20 / 283 (7.07%)	
number of deaths (all causes)	72	107	
number of deaths resulting from adverse events	8	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 270 (0.37%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertension			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders - Other, specify			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 270 (0.37%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Adult respiratory distress syndrome			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary hemorrhage			

subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnea			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations - Other, specify			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications - Other, specify			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal atrial tachycardia			

subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial hemorrhage			
subjects affected / exposed	2 / 270 (0.74%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Syncope			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 270 (0.37%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify			
subjects affected / exposed	0 / 270 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 270 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 270 (1.11%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	8 / 270 (2.96%)	5 / 283 (1.77%)	
occurrences causally related to treatment / all	5 / 8	1 / 5	
deaths causally related to treatment / all	2 / 4	0 / 2	
Lung infection			
subjects affected / exposed	6 / 270 (2.22%)	3 / 283 (1.06%)	
occurrences causally related to treatment / all	2 / 6	2 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations - Other, specify			
subjects affected / exposed	1 / 270 (0.37%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Encephalitis infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 270 (0.37%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treosulfan_ Safety Analysis Set	Busulfan_ Safety Analysis Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	250 / 270 (92.59%)	272 / 283 (96.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 270 (13.70%)	60 / 283 (21.20%)	
occurrences (all)	46	75	
Hypotension			
subjects affected / exposed	19 / 270 (7.04%)	12 / 283 (4.24%)	
occurrences (all)	22	13	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	93 / 270 (34.44%)	100 / 283 (35.34%)	
occurrences (all)	138	133	
Edema limbs			
subjects affected / exposed	61 / 270 (22.59%)	38 / 283 (13.43%)	
occurrences (all)	75	53	
Fatigue			
subjects affected / exposed	33 / 270 (12.22%)	35 / 283 (12.37%)	
occurrences (all)	36	40	
Chills			

subjects affected / exposed	20 / 270 (7.41%)	16 / 283 (5.65%)	
occurrences (all)	25	17	
Localized edema			
subjects affected / exposed	16 / 270 (5.93%)	14 / 283 (4.95%)	
occurrences (all)	18	17	
Pain			
subjects affected / exposed	16 / 270 (5.93%)	8 / 283 (2.83%)	
occurrences (all)	19	11	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	15 / 270 (5.56%)	22 / 283 (7.77%)	
occurrences (all)	20	22	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	18 / 270 (6.67%)	22 / 283 (7.77%)	
occurrences (all)	23	24	
Dyspnea			
subjects affected / exposed	14 / 270 (5.19%)	22 / 283 (7.77%)	
occurrences (all)	17	22	
Investigations			
GGT increased			
subjects affected / exposed	20 / 270 (7.41%)	34 / 283 (12.01%)	
occurrences (all)	22	44	
Blood bilirubin increased			
subjects affected / exposed	25 / 270 (9.26%)	18 / 283 (6.36%)	
occurrences (all)	37	19	
Alanine aminotransferase increased			
subjects affected / exposed	23 / 270 (8.52%)	18 / 283 (6.36%)	
occurrences (all)	24	23	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 270 (8.52%)	14 / 283 (4.95%)	
occurrences (all)	23	15	
Investigations - Other, specify			
subjects affected / exposed	19 / 270 (7.04%)	18 / 283 (6.36%)	
occurrences (all)	19	19	
Weight gain			

subjects affected / exposed	19 / 270 (7.04%)	18 / 283 (6.36%)	
occurrences (all)	22	19	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 270 (16.30%)	52 / 283 (18.37%)	
occurrences (all)	54	64	
Dizziness			
subjects affected / exposed	17 / 270 (6.30%)	14 / 283 (4.95%)	
occurrences (all)	17	16	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	40 / 270 (14.81%)	31 / 283 (10.95%)	
occurrences (all)	48	33	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	12 / 270 (4.44%)	24 / 283 (8.48%)	
occurrences (all)	12	28	
Gastrointestinal disorders			
Mucositis oral			
subjects affected / exposed	102 / 270 (37.78%)	135 / 283 (47.70%)	
occurrences (all)	125	186	
Nausea			
subjects affected / exposed	89 / 270 (32.96%)	116 / 283 (40.99%)	
occurrences (all)	120	161	
Vomiting			
subjects affected / exposed	59 / 270 (21.85%)	55 / 283 (19.43%)	
occurrences (all)	81	81	
Diarrhea			
subjects affected / exposed	43 / 270 (15.93%)	52 / 283 (18.37%)	
occurrences (all)	53	69	
Constipation			
subjects affected / exposed	33 / 270 (12.22%)	33 / 283 (11.66%)	
occurrences (all)	36	44	
Abdominal pain			
subjects affected / exposed	29 / 270 (10.74%)	28 / 283 (9.89%)	
occurrences (all)	30	34	
Skin and subcutaneous tissue disorders			

Rash maculo-papular			
subjects affected / exposed	32 / 270 (11.85%)	25 / 283 (8.83%)	
occurrences (all)	37	32	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	20 / 270 (7.41%)	22 / 283 (7.77%)	
occurrences (all)	27	29	
Pruritus			
subjects affected / exposed	16 / 270 (5.93%)	12 / 283 (4.24%)	
occurrences (all)	19	12	
Purpura			
subjects affected / exposed	14 / 270 (5.19%)	10 / 283 (3.53%)	
occurrences (all)	19	10	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	40 / 270 (14.81%)	37 / 283 (13.07%)	
occurrences (all)	47	42	
Bone pain			
subjects affected / exposed	37 / 270 (13.70%)	28 / 283 (9.89%)	
occurrences (all)	43	29	
Arthralgia			
subjects affected / exposed	27 / 270 (10.00%)	10 / 283 (3.53%)	
occurrences (all)	34	13	
Pain in extremity			
subjects affected / exposed	23 / 270 (8.52%)	11 / 283 (3.89%)	
occurrences (all)	29	15	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	25 / 270 (9.26%)	26 / 283 (9.19%)	
occurrences (all)	34	31	
Catheter related infection			
subjects affected / exposed	14 / 270 (5.19%)	9 / 283 (3.18%)	
occurrences (all)	14	9	
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	24 / 270 (8.89%)	26 / 283 (9.19%)	
occurrences (all)	25	28	
Hypomagnesemia			
subjects affected / exposed	14 / 270 (5.19%)	8 / 283 (2.83%)	
occurrences (all)	16	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2013	Modifications were recommended by the DMC after evaluation of the first planned interim analysis and the trial was newly set up after protocol amendment 03. The dose of the test arm was reduced from 3 x 14 g/m² Treosulfan to 3 x 10 g/m². In addition, the treatment regimen of the test arm was changed so that administration of both test and reference drug was started the same day (Day -4 prior to allogeneic HSCT). Moreover, the follow-up period of transplanted patients was extended from 1 year to 2 years after Transplantation, the sample size increased and the statistical planning revised. Due to the substantial changes, previously enrolled patients (part 1) were not included in the statistical analysis. Thus, the modified new part of the study reported here (part 2) has to be considered an independent study.
10 July 2015	The responsibilities for planned statistical interim analyses and DMC reports were transferred to an independent contract research organisation. A new pharmacokinetic sub-study was to be implemented and conducted at one German site due to dose reduction of Treosulfan after amendment 03 and newly available bioanalytical methods for Treosulfan and epoxide detection. Further minor changes were made to promote future study conduct, monitoring and documentation, including the reduction of protocol appendices. For a better comprehensibility, all paragraphs related to protocol versions prior to amendment 03 were deleted. The patient information was revised to include an update of the Summary of product characteristic (SmPC) of the comparator Busilvex®. An additional patient information and informed consent form was provided for the site that was to perform the pharmacokinetic sub-study.
02 December 2016	The CRO contracted for trial conduct was replaced with another CRO. Textual changes were made to country specific clinical trial protocols in order to provide one integrated protocol for all countries. It was clarified that the DMC was to meet on a yearly basis after the trial is open to patient enrolment until the last patient enrolled had been treated. Thereafter, no changes in trial conduct could result from DMC recommendations. In addition the DMC was to meet at the pre-specified time points of confirmatory efficacy analyses. The range of permissible IMP dose deviation (previously < 10%) was aligned with the exclusion criteria of patients from the Per Protocol Set (PPS) (deviation of at most plus/minus 20%). For the initial examinations it was clarified that it is sufficient to measure either diffusing capacity of the lung for carbon monoxide (DLCOS) Hb-adjusted or forced expiratory volume 1 second (FEV1). Mucositis was considered a significant adverse event in trial MC-FludT.14/L. Although differently described in the Clinical Trial Protocol, confirmatory superiority testing was not planned for the event 'mucositis'. Relevant sections of the Clinical Trial Protocol were revised. The definition of engraftment after HSCT was clarified in order to avoid misinterpretations. The Investigational Medicinal Product Dossier (IMPD) was updated and submitted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 September 2012	The trial had already been registered in the EudraCT data base on 21-April-2008 with first patient in on 24-NOV-2008. Following the recommendation of the independent DMC the MC-FludT.14/L trial was temporarily suspended to accrual. This modification was recommended by the DMC, because of concerns about prolonged neutropenia and subsequent serious infectious complications in the Treosulfan group. Due to substantial protocol changes, all previously enrolled patients (Part I) were not included in the statistical analysis of trial data collected after re-activation. Accordingly, the final results provided are based exclusively on the 570 patients randomized after protocol amendment 03 including post-surveillance follow-up of surviving patients. An overview about the final results for patients enrolled before protocol amendment 03 (Part I) are given in the synopsis uploaded to this EudraCT record.	13 June 2013

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The final results provided here are based exclusively on the 570 patients randomized after protocol amendment 03.
Final results for patients enrolled before protocol amendment 03 (Part I) are given in the synopsis uploaded to this EudraCT record.

Notes: