Clinical trial results:
Clinical phase 2 trial to compare treosulfan-based conditioning therapy with busulfan-based conditioning prior to allogeneic haematopoietic stem cell transplantation (HSCT) in paediatric patients with non-malignant diseases.

Summary

EudraCT number	2013-005508-33
Trial protocol	DE AT CZ PL IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	03 April 2022
First version publication date	03 April 2022

Trial information

Trial identification

Sponsor protocol code	MC-FludT.16/NM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02349906
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	medac Gesellschaft fuer klinische Spezialpraeparate mbH
Sponsor organisation address	Theaterstrasse 6, Wedel, Germany, 22880
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Scientific contact	Medical Expert, medac Gesellschaft fuer klinische Spezialpräparate mbH, 0049 410380060, medwiss@medac.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000088-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	07 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to describe the safety and efficacy of i.v. treosulfan compared to the conventional (myeloablative) dose of i.v. busulfan, each administered as part of a standardised fludarabine-containing conditioning regimen and to contribute to a 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
The primary objective of this trial was the comparative evaluation of freedom from transplantation (treatment)-related mortality, defined as death from any transplantation (treatment)-related cause from start of conditioning treatment (visit Day -7) until day +100 after HSCT.

Protection of trial subjects:

The study was conducted in accordance with ICH GCP guidelines, applicable local laws and in compliance with the ethical principles originating in the Declaration of Helsinki.
Regulatory authorities were informed of the study and amendments in accordance with national regulations and, where necessary, the appropriate approval was obtained.
Due to the life-threatening diseases to be treated, an independent Data Monitoring Committee (DMC) was set up. All available safety and efficacy data were subjected to thorough review.

Background therapy:

This trial allowed administration of 2 different background conditioning regimens in addition to treosulfan or busulfan: one background conditioning regimen consisted of an intensified fludarabine-containing regimen with additional thiotepa (Stratum A) whereas the other consisted of the standard regimen with fludarabine only (Stratum B).
Other concomitant medication could be administered according to the hospital practice.

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.

Actual start date of recruitment	20 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, 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: 34
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Italy: 22
Worldwide total number of subjects	106
EEA total number of subjects	106

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)	29
Children (2-11 years)	61
Adolescents (12-17 years)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

106 subjects were enrolled at 18 sites in 4 countries.
The first subject was enrolled in the study on 20 April 2015.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the study to ensure that all subjects met all inclusion and exclusion criteria.
A total of 106 subjects were randomised of which 101 subjects received Investigational medicinal product (IMP) and were included in the efficacy and safety analyses.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Due to the different treatment schedules of the test arm (treosulfan) and the reference arm (busulfan) with regard to the different infusion regimens, blinding of the IMP was not considered feasible within the orphan indication of paediatric subjects with a non-malignant indication for allogeneic HSCT.

Arms

Are arms mutually exclusive?	Yes
Arm title	Busulfan

Arm description:

This arm comprises all subjects randomised to Busulfan.

Arm type	Active comparator
Investigational medicinal product name	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 was administered i.v. on 4 consecutive days (days -7, -6, -5, and -4) prior to Hematopoietic stem-cell transplantation (HSCT) (day 0). Busulfan was to be infused in accordance with the respective hospital standard, ie, 1, 2, or 4 times daily. The required total dose was calculated on basis of the actual body weight based on the summary of product characteristics (SmPC).

Arm title	Treosulfan

Arm description:

This arm comprises all subjects randomised to Treosulfan.

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

Dosage and administration details:

Treosulfan was administered i.v. over 2 hours on 3 consecutive days (days -6, -5, and -4) prior to HSCT (day 0). The required total dose of treosulfan was calculated on basis of the subject’s body surface area (BSA).

Number of subjects in period 1	Busulfan	Treosulfan
Started	54	52
Completed	50	51
Not completed	4	1
Withdrawal prior to start of treatment with IMP	4	1

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Busulfan

Arm description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to busulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

Arm type	Active comparator
Investigational medicinal product name	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 was administered i.v. on 4 consecutive days (days -7, -6, -5, and -4) prior to Hematopoietic stem-cell transplantation (HSCT) (day 0). Busulfan was to be infused in accordance with the respective hospital standard, ie, 1, 2, or 4 times daily. The required total dose was calculated on basis of the actual body weight based on the summary of product characteristics (SmPC) for Busilvex.

Arm title	Treosulfan

Arm description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to treosulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

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

Dosage and administration details:

Treosulfan was administered i.v. over 2 hours on 3 consecutive days (days -6, -5, and -4) prior to HSCT (day 0). The required total dose of treosulfan was calculated on basis of the subject's body surface area (BSA).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: To be able to document the reason for "not complete" between randomization and treatment for both treatment arms separately, an additional pretreatment ("Randomization") period was created.

Number of subjects in period 2[2]	Busulfan	Treosulfan
Started	50	51
Completed	43	47
Not completed	7	4
Death	7	2
Lost to follow-up	-	2

Notes:

[2] - 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 is based on the subjects treated (Full Analysis set).

Baseline characteristics

Reporting groups

Reporting group title	Busulfan

Reporting group description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to busulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

Reporting group title	Treosulfan

Reporting group description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to treosulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

Reporting group values	Busulfan	Treosulfan	Total
Number of subjects	50	51	101
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	14	14	28
Children (2-11 years)	26	31	57
Adolescents (12-17 years)	10	6	16
Age continuous Units: years			
arithmetic mean	6.0	5.0	
standard deviation	± 5.3	± 4.4	-
Gender categorical Units: Subjects			
Female	19	15	34
Male	31	36	67
Summary of trial disease characteristics Units: Subjects			
Primary immunodeficiencies	28	23	51
Inborn errors metabolism	4	2	6
Hemoglobinopathies	13	21	34
Bone marrow failure syndromes	5	5	10
Donor type Units: Subjects			
Matched sibling donor (MSD)	12	9	21
Matched family donor (MFD)	5	5	10
Matched unrelated donor (MUD)	32	36	68
Umbilical cord blood (UCB)	1	1	2
Body surface area Units: square meter			
arithmetic mean	0.836	0.746	
standard deviation	± 0.396	± 0.297	-

End points

End points reporting groups

Reporting group title	Busulfan

Reporting group description:

This arm comprises all subjects randomised to Busulfan.

Reporting group title	Treosulfan

Reporting group description:

This arm comprises all subjects randomised to Treosulfan.

Reporting group title	Busulfan

Reporting group description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to busulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

Reporting group title	Treosulfan

Reporting group description:

This arm is equal to the Full Analysis Set (FAS) and includes all subjects randomised to treosulfan who received at least one dose of the IMP and with at least one documented efficacy parameter.
The subjects within the FAS were analysed in their initial arm of randomisation (intention to treat principle).

Subject analysis set title	Treosulfan Pharmacokinetic Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled analysis of MC FludT16/NM and MC FludT.17/M.
The PK Set included all subjects of the FAS with any treosulfan concentration measurements.

Primary: Freedom from transplantation (treatment)-related mortality - Number

End point title	Freedom from transplantation (treatment)-related mortality - Number[1]

End point description:

Freedom from transplantation (treatment)-related mortality, defined as death from any transplantation (treatment)-related cause from start of conditioning treatment (visit Day -7) until day +100 after HSCT. The associated time span of transplantation-related mortality was defined as the interval from end of HSCT to death due to transplantation-related cause whereas the time span of treatment-related mortality was defined as interval from start of conditioning treatment, ie, visit Day -7, until end of 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: The data analysis is descriptive in nature. No specific confirmatory statistical hypotheses are specified.

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: Subjects				
With event	5	0		
Without event	45	51		

Statistical analyses

No statistical analyses for this end point

Primary: Freedom from transplantation (treatment)-related mortality - Incidence

End point title	Freedom from transplantation (treatment)-related mortality - Incidence

End point description:

Incidence of freedom from transplantation (treatment)-related mortality, defined as death from any transplantation (treatment)-related cause from start of conditioning treatment (visit Day -7) until day +100 after HSCT.
The associated time span of transplantation-related mortality was defined as the interval from end of HSCT to death due to transplantation-related cause whereas the time span of treatment-related mortality was defined as interval from start of conditioning treatment, ie, visit Day -7, until end of HSCT.

End point type	Primary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)	90.0 (80.1 to 96.0)	100.0 (94.3 to 100.0)		

Statistical analyses

Statistical analysis title	Diff. incidences
Comparison groups	Busulfan v Treosulfan
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0528
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-10
Confidence interval	
level	90 %
sides	2-sided
lower limit	-19.9
upper limit	-3.4

Secondary: Engraftment - reconstitution of granulopoiesis

End point title	Engraftment - reconstitution of granulopoiesis

End point description:

Neutrophilic granulocytes engraftment was assessed by reconstitution of granulopoiesis.
Engraftment was defined as the first of 3 consecutive days with an absolute neutrophilic granulocytes count of more than 0.5 x10^9/L. The term "consecutive days" was defined as 3 consecutive blood samples if taken on different days.
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.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)	100.0 (94.1 to 100.0)	97.3 (88.7 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Engraftment - reconstitution of leukopoiesis

End point title	Engraftment - reconstitution of leukopoiesis

End point description:

Leukocyte engraftment was assessed by reconstitution of leukopoiesis.
Engraftment was defined as the first of 3 consecutive days with a total leucocyte of more than 1 x 10^9/L. The term "consecutive days" was defined as 3 consecutive blood samples if taken on different days.
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.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)	100.0 (94.1 to 100.0)	96.8 (87.1 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Engraftment - reconstitution of thrombopoiesis > 20 x10^9/L

End point title	Engraftment - reconstitution of thrombopoiesis > 20 x10^9/L

End point description:

Platelet (PLT) engraftment was assessed by reconstitution of thrombopoiesis.
Engraftment was defined as the first of 3 consecutive days with PLT count of at least 20 x10^9/L in the absence of PLT transfusion. The term "consecutive days" was defined as 3 consecutive blood samples if taken on different days.
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.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)	96.8 (86.6 to 100.0)	100.0 (93.8 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Engraftment - reconstitution of thrombopoiesis > 50 x10^9/L

End point title	Engraftment - reconstitution of thrombopoiesis > 50 x10^9/L

End point description:

Platelet (PLT) engraftment was assessed by reconstitution of thrombopoiesis.
Engraftment was defined as the first of 3 consecutive days with PLT count of at least 50 x10^9/L in the absence of PLT transfusion. The term "consecutive days" was defined as 3 consecutive blood samples if taken on different days.
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.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)	97.1 (87.9 to 100.0)	94.8 (86.3 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: HSOS, lung toxicity, hepatic toxicity, early toxicity (until day +28) and infections of any CTCAE grade

End point title	HSOS, lung toxicity, hepatic toxicity, early toxicity (until day +28) and infections of any CTCAE grade

End point description:

Incidence of all treatment emergent significant adverse events.
Evaluation of hepatic sinusoidal obstruction syndrome ("HSOS", according to Jones et al), "Lung toxicity" (CTCAE term "Pulmonary fibrosis"), "Hepatic toxicity" (according to Bearman's criteria), Early toxicity defined as any AE occurring until day +28 and "Infections of any CTCAE grade" (non-serious and serious) until day +100.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
HSOS according to Jones (1987)	10.0 (4.0 to 19.9)	2.0 (0.1 to 9.0)		
Early toxicity (any AE occurring until day +28)	96.0 (87.9 to 99.3)	94.1 (85.5 to 98.4)		
Hepatic toxicity according to Bearman (1988)	54.0 (41.5 to 66.2)	51.0 (38.7 to 63.2)		
Lung toxicity (CTCAE term "Pulmonary fibrosis")	0.0 (0.0 to 5.8)	0.0 (0.0 to 5.7)		
Infections (SOC "Infections and infestations")	70.0 (57.6 to 80.5)	60.8 (48.3 to 72.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of complete donor type chimerism

End point title	Incidence of complete donor type chimerism

End point description:

Evaluation of donor-type chimerism on day +28, day +100, and 12 months after HSCT.
Chimerism was analysed in Peripheral blood or Bone marrow samples at visits Day +28, Day +100, Month 12.
Complete donor-type chimerism was defined if a value of >= 95% was 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:

28 days, 100 days and 12 months after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[2]	51[3]		
Units: percent				
number (confidence interval 90%)				
Day +28	82.0 (70.7 to 90.3)	84.3 (73.5 to 91.9)		
Day +100	84.8 (73.3 to 92.6)	66.7 (54.3 to 77.5)		
Month 12	76.7 (63.8 to 86.8)	49.0 (36.5 to 61.5)		

Notes:

[2] - Subjects at risk:
Day +28 = 50
Day +100 = 46
Month 12 = 43

[3] - Subjects at risk:
Day +28 = 51
Day +100 = 51
Month 12 = 49

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

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	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
Month 12	88.0 (77.9 to 93.7)	96.1 (88.0 to 98.8)		
Month 24	88.0 (77.9 to 93.7)	96.1 (88.0 to 98.8)		
Month 36	84.0 (71.4 to 91.4)	96.1 (88.0 to 98.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of graft failure

End point title	Incidence of graft failure

End point description:

The incidence of graft failure was defined as the probability of having a graft failure (primary or secondary) and being alive without using “stem cell infusion (re-transplant) with conditioning” rescue therapy (ie, second allogenic transplantations) between the end of HSCT and the end of the longer term follow up phase.
The associated time span was defined as the interval from day 0 to graft failure.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
Month 12	4.0 (0.0 to 8.6)	15.8 (7.4 to 24.3)		
Month 24	4.0 (0.0 to 8.6)	21.0 (11.2 to 30.9)		
Month 36	4.0 (0.0 to 8.6)	24.8 (13.6 to 35.9)		

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 aGvHD was defined as the time between end of HSCT and the date of first occurrence of aGvHD. Subjects alive with no occurrence of aGvHD at 100 days after end of HSCT and no competing event were censored. Death and graft failure within 100 days after HSCT were competing events.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: Subjects				
With event	21	28		
Without event	29	23		

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 aGvHD was defined as the time between end of HSCT and the date of first occurrence of aGvHD. Subjects alive with no occurrence of aGvHD at 100 days after end of HSCT and no competing event were censored. Death and graft failure within 100 days after HSCT were competing events.

End point type	Secondary

End point timeframe:

14, 28 and 100 days after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
Day 14	2.0 (0.0 to 5.3)	13.7 (5.8 to 21.7)		
Day 28	30.0 (19.3 to 40.7)	37.3 (26.1 to 48.4)		
Day 100	42.0 (30.5 to 53.5)	54.9 (43.4 to 66.4)		

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 aGvHD was defined as the time between end of HSCT and the date of first occurrence of aGvHD. Subjects alive with no occurrence of aGvHD at 100 days after end of HSCT and no competing event were censored. Death and graft failure within 100 days after HSCT were competing events.

End point type	Secondary

End point timeframe:

Until day +100 after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: subjects				
With event	4	7		
Without event	46	44		

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:

14, 28 and 100 days after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
Day 14	2.0 (0.0 to 5.3)	2.0 (0.0 to 5.2)		
Day 28	4.0 (0.0 to 8.6)	2.0 (0.0 to 5.2)		
Day 100	8.0 (1.7 to 14.3)	13.7 (5.8 to 21.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall chronic GvHD - number

End point title	Overall chronic GvHD - number

End point description:

Overall chronic graft versus host disease - number of subjects with and without event.
Chronic GvHD was evaluated from 100 days after transplantation until the end of the longer term follow-up. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD.
Subjects were at risk (evaluable) for cGvHD if they had survived graft failure-free until 100 days after end of HSCT. In addition, subjects with premature trial termination at visit Day +100 were excluded from the risk set. Subjects alive with no cGvHD at the last follow-up were censored.
Death and graft failure were competing events.

End point type	Secondary

End point timeframe:

From day +100 to last follow-up visit

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: subjects				
With event	17	6		
Without event	27	41		

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:

Overall chronic graft versus host disease - cumulative incidence
Chronic GvHD was evaluated from 100 days after transplantation until the end of the longer term follow-up. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD.
Subjects were at risk (evaluable) for cGvHD if they had survived graft failure-free until 100 days after end of HSCT. In addition, subjects with premature trial termination at visit Day +100 were excluded from the risk set. Subjects alive with no cGvHD at the last follow-up were censored.
Death and graft failure were competing events

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: percent				
number (confidence interval 90%)				
Month 12	38.6 (26.6 to 50.7)	12.8 (4.8 to 20.8)		
Month 24	38.6 (26.6 to 50.7)	12.8 (4.8 to 20.8)		
Month 36	38.6 (26.6 to 50.7)	12.8 (4.8 to 20.8)		

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/severe chronic graft versus host disease - number of subjects with and without event.
Chronic GvHD was evaluated from 100 days after transplantation until the end of the longer term follow-up. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD.
Subjects were at risk (evaluable) for cGvHD if they had survived graft failure-free until 100 days after end of HSCT. In addition, subjects with premature trial termination at visit Day +100 were excluded from the risk set. Subjects alive with no cGvHD at the last follow-up were censored.
Death and graft failure were competing events

End point type	Secondary

End point timeframe:

From day +100 to last follow-up visit

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: subjects				
With event	10	5		
Without event	34	42		

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.
Chronic GvHD was evaluated from 100 days after transplantation until the end of the longer term follow-up. Time to cGvHD was defined as the time between 100 days after end of HSCT and the first episode of cGvHD.
Subjects were at risk (evaluable) for cGvHD if they had survived graft failure-free until 100 days after end of HSCT. In addition, subjects with premature trial termination at visit Day +100 were excluded from the risk set. Subjects alive with no cGvHD at the last follow-up were censored.
Death and graft failure were competing events.

End point type	Secondary

End point timeframe:

12, 24 and 36 months after HSCT

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: percent				
number (confidence interval 90%)				
Month 12	22.7 (12.3 to 33.1)	10.6 (3.2 to 18.0)		
Month 24	22.7 (12.3 to 33.1)	10.6 (3.2 to 18.0)		
Month 36	22.7 (12.3 to 33.1)	10.6 (3.2 to 18.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue therapies

End point title	Use of rescue therapies

End point description:

Rescue therapies, cell therapies given in order to treat acute graft failure or relapse of the underlying disease were to be documented as rescue therapies. These included unfractionated or fractionated (eg, allo-depleted or T-cell receptor alpha-beta depleted) donor lymphocyte infusions (DLI) and stem cell infusions (SCI) with or without further conditioning regimens. Re-occurrence of transfusion dependence for red blood cells or PLT was to be documented as rescue therapy.

End point type	Secondary

End point timeframe:

Visit Day 0 (end of HSCT) until the end of the longer term follow up phase.

End point values	Busulfan	Treosulfan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent				
number (confidence interval 90%)				
Any rescue therapy	42.0 (30.1 to 54.6)	41.2 (29.5 to 53.7)		
DLIs	4.0 (0.7 to 12.1)	9.8 (3.9 to 19.5)		
Stem cell boost	2.0 (0.1 to 9.1)	3.9 (0.7 to 11.8)		
SCI (re-transplant) with conditioning	2.0 (0.1 to 9.1)	0.0 (0.0 to 5.7)		
SCI (re-transplant) without conditioning	0.0 (0.0 to 5.8)	0.0 (0.0 to 5.7)		
Transfusion dependence for red blood cells	34.0 (23.0 to 46.5)	33.3 (22.5 to 45.7)		
Transfusion dependence for platelets	28.0 (17.8 to 40.3)	27.5 (17.4 to 39.5)		
Other rescue therapies	4.0 (0.7 to 12.1)	7.8 (2.7 to 17.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK result _ t1/2term

End point title	PK result _ t1/2term

End point description:

Pooled analysis of MC FludT16/NM and MC FludT.17/M.
Pharmacokinetic Parameter t1/2term = apparent terminal elimination half-life.
Analysis of PK parameters was performed in a subset of subjects treated with treosulfan. The calculation of individual treosulfan dose was adapted to the subject’s BSA group.

End point type	Secondary

End point timeframe:

PK samples were taken on day -6 (first day of treatment with treosulfan) at 5 predefined different time points between +/- 5 minutes and 7-8 hours after the end of the infusion.

End point values	Treosulfan Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	82[4]			
Units: hour				
geometric mean (standard deviation)				
BSA group ≤ 0.5 m² (10 g/m² dose group)	1.27 (± 0.178)			
BSA group > 0.5 - ≤ 1.0 m² (12 g/m² dose group)	1.40 (± 0.173)			
BSA group > 1.0 m² (14 g/m² dose group)	1.58 (± 0.178)			

Notes:

[4] - BSA group ≤ 0.5 m²: N = 16
BSA group > 0.5 - ≤ 1.0 m²: N =37
BSA group > 1.0 m²: N = 29

Statistical analyses

No statistical analyses for this end point

Secondary: PK result _ AUC infinity

End point title	PK result _ AUC infinity

End point description:

Pooled analysis of MC FludT16/NM and MC FludT.17/M.
Pharmacokinetic Parameter AUC infinity = AUC from time 0 to infinite time.
Analysis of PK parameters was performed in a subset of subjects treated with treosulfan. The calculation of individual treosulfan dose was adapted to the subject's BSA group.

End point type	Secondary

End point timeframe:

PK samples were taken on day -6 (first day of treatment with treosulfan) at 5 predefined different time points between +/- 5 minutes and 7-8 hours after the end of the infusion.

End point values	Treosulfan Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	81[5]			
Units: µg.h/mL				
geometric mean (standard deviation)				
BSA group ≤ 0.5 m² (10 g/m² dose group)	1570 (± 482)			
BSA group > 0.5 - ≤ 1.0 m² (12 g/m² dose group)	1672 (± 401)			
BSA group > 1.0 m² (14 g/m² dose group)	1903 (± 310)			

Notes:

[5] - BSA group ≤ 0.5 m²: N = 15
BSA group > 0.5 - ≤ 1.0 m²: N =37
BSA group > 1.0 m²: N = 29

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PK result _ Cmax

End point title	PK result _ Cmax

End point description:

Pooled analysis of MC FludT16/NM and MC FludT.17/M.
Pharmacokinetic Parameter Cmax = the maximum observed plasma concentration.
Analysis of PK parameters was performed in a subset of subjects treated with treosulfan. The calculation of individual treosulfan dose was adapted to the subject's BSA group.

End point type	Other pre-specified

End point timeframe:

PK samples were taken on day -6 (first day of treatment with treosulfan) at 5 predefined different time points between +/- 5 minutes and 7-8 hours after the end of the infusion.

End point values	Treosulfan Pharmacokinetic Set			
Subject group type	Subject analysis set			
Number of subjects analysed	82[6]			
Units: µg/mL				
geometric mean (standard deviation)				
BSA group ≤ 0.5 m² (10 g/m² dose group)	608 (± 209)			
BSA group > 0.5 - ≤ 1.0 m² (12 g/m² dose group)	662 (± 286)			
BSA group > 1.0 m² (14 g/m² dose group)	652 (± 111)			

Notes:

[6] - BSA group ≤ 0.5 m²: N = 15
BSA group > 0.5 - ≤ 1.0 m²: N =38
BSA group > 1.0 m²: N = 29

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AE (serious and non serious) occurring between day -7 and day +100 after HSCT were to be reported. Thereafter, only SAE with suspected relatedness (SAR) were to be reported until the end of longer-term follow-up phase.

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 IMP.
All subjects were analysed within their arm of actual treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Busulfan - Safety Analysis Set

Reporting group description:

This arm comprises all subjects who were randomised to Busulfan and received at least one dose of IMP.

Reporting group title	Treosulfan - Safety Analysis Set

Reporting group description:

This arm comprises all subjects randomised to treosulfan who received at least one dose of the IMP.

Serious adverse events	Busulfan - Safety Analysis Set	Treosulfan - Safety Analysis Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 50 (32.00%)	18 / 51 (35.29%)	
number of deaths (all causes)	7	2	
number of deaths resulting from adverse events	4	0	
Investigations			
Investigations - Other, specify			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
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 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 50 (0.00%)	6 / 51 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders - Other, specify			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (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 - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	0 / 50 (0.00%)	5 / 51 (9.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	2 / 50 (4.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Busulfan - Safety Analysis Set	Treosulfan - Safety Analysis Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 50 (96.00%)	49 / 51 (96.08%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 50 (36.00%)	19 / 51 (37.25%)	
occurrences (all)	29	20	
Hematoma			
subjects affected / exposed	6 / 50 (12.00%)	3 / 51 (5.88%)	
occurrences (all)	8	4	
Hypotension			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	6	3	
Capillary leak syndrome			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	36 / 50 (72.00%)	36 / 51 (70.59%)	
occurrences (all)	71	58	
Infusion related reaction			
subjects affected / exposed	6 / 50 (12.00%)	9 / 51 (17.65%)	
occurrences (all)	11	11	
Chills			
subjects affected / exposed	3 / 50 (6.00%)	7 / 51 (13.73%)	
occurrences (all)	3	7	
Localized edema			
subjects affected / exposed	4 / 50 (8.00%)	4 / 51 (7.84%)	
occurrences (all)	4	6	
Fatigue			
subjects affected / exposed	4 / 50 (8.00%)	3 / 51 (5.88%)	
occurrences (all)	8	3	
Pain			
subjects affected / exposed	3 / 50 (6.00%)	4 / 51 (7.84%)	
occurrences (all)	7	5	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	13 / 50 (26.00%)	10 / 51 (19.61%)	
occurrences (all)	19	11	
Epistaxis			
subjects affected / exposed	7 / 50 (14.00%)	8 / 51 (15.69%)	
occurrences (all)	11	9	
Hypoxia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 51 (7.84%)	
occurrences (all)	3	5	
Sore throat			
subjects affected / exposed	2 / 50 (4.00%)	5 / 51 (9.80%)	
occurrences (all)	2	5	
Pharyngeal mucositis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 50 (20.00%)	8 / 51 (15.69%)	
occurrences (all)	13	9	
Investigations - Other, specify			
subjects affected / exposed	4 / 50 (8.00%)	8 / 51 (15.69%)	
occurrences (all)	5	11	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 50 (14.00%)	4 / 51 (7.84%)	
occurrences (all)	9	6	
GGT increased			
subjects affected / exposed	6 / 50 (12.00%)	2 / 51 (3.92%)	
occurrences (all)	6	2	
Blood bilirubin increased			
subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 50 (14.00%)	5 / 51 (9.80%)	
occurrences (all)	9	6	
Sinus bradycardia			

subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 50 (24.00%)	14 / 51 (27.45%)	
occurrences (all)	18	20	
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	3 / 51 (5.88%)	
occurrences (all)	8	3	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 50 (0.00%)	4 / 51 (7.84%)	
occurrences (all)	0	4	
Hemolysis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Eye disorders			
Eye disorders - Other, specify			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Mucositis oral			
subjects affected / exposed	40 / 50 (80.00%)	36 / 51 (70.59%)	
occurrences (all)	43	36	
Vomiting			
subjects affected / exposed	32 / 50 (64.00%)	33 / 51 (64.71%)	
occurrences (all)	71	69	
Diarrhea			
subjects affected / exposed	23 / 50 (46.00%)	30 / 51 (58.82%)	
occurrences (all)	45	46	
Abdominal pain			
subjects affected / exposed	15 / 50 (30.00%)	23 / 51 (45.10%)	
occurrences (all)	25	39	
Nausea			
subjects affected / exposed	19 / 50 (38.00%)	15 / 51 (29.41%)	
occurrences (all)	33	20	
Constipation			

subjects affected / exposed	7 / 50 (14.00%)	8 / 51 (15.69%)	
occurrences (all)	9	13	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	4 / 50 (8.00%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Gastritis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	2	4	
Stomach pain			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Anal mucositis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify			
subjects affected / exposed	28 / 50 (56.00%)	26 / 51 (50.98%)	
occurrences (all)	41	36	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 50 (18.00%)	14 / 51 (27.45%)	
occurrences (all)	11	22	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	9 / 50 (18.00%)	13 / 51 (25.49%)	
occurrences (all)	12	24	
Rash maculo-papular			
subjects affected / exposed	7 / 50 (14.00%)	13 / 51 (25.49%)	
occurrences (all)	8	20	
Alopecia			
subjects affected / exposed	6 / 50 (12.00%)	11 / 51 (21.57%)	
occurrences (all)	6	11	
Dry skin			
subjects affected / exposed	5 / 50 (10.00%)	0 / 51 (0.00%)	
occurrences (all)	5	0	
Skin hyperpigmentation			

subjects affected / exposed	3 / 50 (6.00%)	2 / 51 (3.92%)	
occurrences (all)	3	2	
Urticaria			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Hypertrichosis			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	5 / 50 (10.00%)	5 / 51 (9.80%)	
occurrences (all)	6	5	
Urinary frequency			
subjects affected / exposed	1 / 50 (2.00%)	4 / 51 (7.84%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 50 (12.00%)	9 / 51 (17.65%)	
occurrences (all)	10	11	
Back pain			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	21 / 50 (42.00%)	22 / 51 (43.14%)	
occurrences (all)	40	31	
Rhinitis infective			
subjects affected / exposed	6 / 50 (12.00%)	4 / 51 (7.84%)	
occurrences (all)	6	6	
Sepsis			
subjects affected / exposed	3 / 50 (6.00%)	2 / 51 (3.92%)	
occurrences (all)	3	2	
Lung infection			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Catheter related infection			

subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Skin infection			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Iron overload			
subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Hyperkalemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	6	4	
Hypokalemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2015	Update of the study timelines due to delayed study start Clarification on withdrawal of patients who violate eligibility criteria prior to administration of IMP, i.e. withdrawals without IMP had to be replaced. To ensure that the inclusion/exclusion criteria remain fulfilled until start of conditioning the most current result had to be used for assessment of eligibility in case of repeated examinations. Exclusion criterion number 8 was revised. Clarification of the period in which the patient registration had to be performed. New safety information was added to the protocol and the patient information for parents. Reference to the document "Development Summary of Product Characteristics" for Treograft was added. A narrower therapeutic window range has been defined for a target AUCday0-4 in order to ensure a dose-adjustment of the full myeloablative dose in case Therapeutic drug monitoring of Busulfan has to be performed. The wording for the administration time of i.v. treosulfan and i.v. fludarabine was changed from "within" 120/30 minutes to "over" 120/30 minutes. In addition to prophylactic also therapeutic treatment of GvHD (eg,glucocorticoids) and anti-infective medication administered for anti-bacterial, antiviral and anti-fungal prophylactic treatment had to be documented on the CRF . Exceptions from expedited SAE/SAR reporting, clarification regarding documentation of laboratory parameters as adverse events, detailed instructions on SAE reporting and Instructions on documentation of "pregnancy" as SAE were added. A separate SAE report form has to be completed for each SAE. A change in the number of patients subjected to blood samples has been implemented in case an interim analysis reveals that the population PK model is not sufficiently accurate, or the DMC recommend dose modifications. The accepted time deviation of the first PK sample has been defined. "Graft failure" has been additionally considered as a competing event for aGvHD and cGvHD.
23 June 2016	Changes in Sponsor personnel and job titles. Changes in timelines. Up-to-date information regarding safety was provided in the Investigator's Brochure (approved edition 9.0, released 29-Nov-2015), including the Development SmPC for treosulfan, and in the SmPC for Busilvex. Safety information was deleted from the Clinical Trial Protocol. Additional blood samples were required for the validation of the POP-PK model. Based on a DMC recommendation dated 15-Apr-2016, PK sampling was to be performed until adequate PK data were available for each of the age groups. Editorial changes to improve readability were made and the sentences referring to the pooled statistical analysis and the interim analyses were moved. Subject Information Sheets were updated according to the above mentioned changes.

13 February 2017	The CRO for regulatory aspects and/or monitoring outside of DE changed. In addition, the outsourcing was extended to all countries involved in the clinical trial and to project management. The Sponsor's staff changed. In addition, a Medical Expert was named in order to provide a single point of contact to advise on trial related medical questions or problems. Functions of the International Coordinating Investigator and the National Coordinating Investigators were specified. The definition of engraftment after HSCT was clarified in order to avoid misinterpretations. The term "consecutive days" was defined as 3 consecutive blood samples, if these were taken on different days. The second and third samples were required to confirm stable engraftment above the defined thresholds and were to be taken on the next consecutive days whenever possible; however, exceptions were accepted. Update and submission of the Investigational Medicinal Product Dossier.
06 June 2017	For particular non-malignant diseases like thalassaemia major or combined immunodeficiencies the reoccurrence of disease due to loss of donor cells may require the regular administration of blood products (eg, erythrocytes or PLT) as therapeutic agents. Thus, a return to transfusion dependence associated with the reoccurrence of the underlying disease after allo-HSCT was to be documented as rescue therapy on the CRF. Further, stem cell infusions with or without further conditioning regimens could be used as rescue therapy. A PIP modification was approved requesting to change the requirement to treat the vast majority of subjects (at least 85 out of 100) without additional use of thiotepa. Instead the unlimited use of the thiotepa containing therapy in qualified subjects was permitted. The last regular chimerism documentation (without signs of graft failure) was to be done 12 months after transplantation. The use of rescue therapy and graft failure was to be documented until the end of the longer-term follow-up phase. A donor type chimerism analysis was only required in order to confirm secondary graft failure after sustained decline of neutrophils (≤ 0.5 x 109/L) and leucocytes (≤ 1.0 x 109/L). In some non-malignant diseases like thalassaemia major, graft failure may not manifest as marrow aplasia, but as autologous reconstitution. In these cases, conventional definitions of graft failure based on the detection of cytopaenia could not be applied, but loss of chimerism was the sign of graft failure. Loss of chimerism in the cell compartment of interest led to recurrence of disease symptoms; loss of chimerism in the red cell compartment led to haemolysis and transfusion dependence in thalassaemia. In order to get clear evidence for a late secondary graft failure, the analysis of donor type chimerism was extended to the longer term follow-up phase. The definition of primary graft failure was specified as a donor-type chimerism of < 10% in BM.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported