1 TITLE PAGE

Clinical Study Report

Final Analysis of 330 Patients
included into the clinical study MC-FludT.14/L before Amendment No. 03 was effective

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

Project number:	MC-FludT.14/L
Drug name:	Treosulfan
Indication:	Conditioning treatment prior to haematopoietic stem cell transplantation
Phase:	Phase III
EudraCT number:	2008-002356-18
Date first patient in:	24-Nov-2008
Date last patient out:	26-Sep-2012
Version and date of the report:	Final Version 2.0, 30-Jun-2017
Date of any previous reports:	Final Version 1.0, 03-Mar-2016
Sponsor:	medac Gesellschaft fuer klinische Spezialpraeparate mbH Theaterstr. 6, 22880 Wedel, Germany
Coordinating Investigator:	**Prof. Dietrich W. Beelen, MD** [redacted]
Sponsor's Responsible Medical Officer:	**Dr.** [redacted] **MD**

2 SYNOPSIS

Name of Sponsor: medac Gesellschaft fuer klinische Spezialpraeparate mbH Theaterstr 6, 22880Wedel, Germany	
Name of finished product: Treograft®	
Name of active ingredient: Treosulfan	
Title of study:	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 acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) considered ineligible to standard conditioning regimens
Investigators:	Coordinating Investigator: Prof. Dietrich W. Beelen, MD Principal investigator(s): [redacted]
Study centre(s):	The clinical study was performed in one centre in Finland, three centres in France, nine centres in Germany, one centre in Hungary, four centres in Italy, and two centres in Poland. [redacted] Klinik für Knochenmarktransplantation, Universitätsklinikum Essen, Hufelandstr. 55, 45122 Essen, Germany [redacted] Klinikum Nürnberg (Nord), 5. Medizinische Klinik, Einheit für Knochenmarktransplantation, Prof.-Ernst-Nathan-Str. 1, Haus 12, 90419 Nürnberg, Germany [redacted] Klinikum der Universität Regensburg, Medizinische Klinik I, KMT, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany [redacted] Universitätsklinikum Heidelberg, Innere Medizin V, Hämatologie, Onkologie und Rheumatologie, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany [redacted] Universität Rostock, Klinik für Innere Medizin, Hämatologie/Onkologie, Ernst-Heydemann-Str. 6, 18057 Rostock, Germany [redacted] Klinikum Oldenburg gGmbH, Klinik für Onkologie und Hämatologie, Rahel-Straus-Str. 10, 26133 Oldenburg, Germany [redacted] Universität Tübingen, Medizinische Universitätsklinik II, Allogene Stammzelltransplantation, Hämatologie/Onkologie, Otfried-Müller-Str. 10, 72076 Tübingen, Germany [redacted] Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Zentrum für Innere Medizin, Oberdürrbacher Str. 6, 97080 Würzburg, Germany [redacted] Scientific Institute H. San Raffaele, Hematology and BMT Unit, Dipartimento di Oncoematologia, U.O. Ematologia e TMO, Via Olgettina 60, 20132 Milan, Italy [redacted] A. O. Ospedale Riuniti di Bergamo, Dipartimento di Ematologia e TMO, Largo Barozzi 1, 24127 Bergamo, Italy [redacted] Silesian Medical University, University Department of Haematology and BMT, Dąbrowskiego 25 Str., 40-032 Katowice / 8 Reymonta, 40-029 Katowice, Poland

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Publication (reference):	None.
Studied period (years):	Date of first enrolment: 24-Nov-2008 Date of last completed: 26-Sep-2012
Phase of development:	Phase III
Objectives:	
Primary:	The aim of the study was to compare event-free survival within one year after transplantation between Treosulfan-based conditioning and Busulfan-based conditioning. Events were defined as relapse of disease, graft failure, or death (whatever occurred first).
Secondary:	1. Comparative evaluation of incidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade III/IV mucositis/stomatitis between Day -6 and Day +28 2. Comparative evaluation of overall survival (OS) and cumulative incidence of relapse (RI), non-relapse mortality (NRM) and transplantation related mortality (TRM) 3. Comparative evaluation of Day +28 conditional cumulative incidence of engraftment 4. Comparative evaluation of Day +28 and Day +100 incidence of complete donor-type chimerism 5. Comparative evaluation of cumulative incidence of acute and chronic Graft-versus-Host Disease (GvHD) 6. Comparative evaluation of incidence of other CTCAE Grade III/IV adverse events between Day -6 and Day +28
Methodology:	This trial was designed as a randomised, parallel-group, open label, multicentre, international, group-sequential phase III non-inferiority trial.
Number of patients (planned and analysed):	planned: 545 enrolled: 330 withdrawn: 10 completed: 320 Full Analysis Set: 320 Safety Analysis Set: 320 Per Protocol Set: 305
Diagnosis and main criteria for inclusion:	**Inclusion Criteria** 1. Patients with acute myeloid leukaemia acc. to World Health Organisation (WHO), 2001 (AML in complete remission [CR] at transplant, i.e. blast counts <5% in bone marrow) or myelodysplastic syndrome acc. to WHO, 2001 (MDS with blast counts <20% in bone marrow during disease

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history) indicated for allogeneic haematopoietic progenitor cell transplantation but considered to be at increased risk for standard conditioning therapies according to the following criteria:

- patients aged ≥ 50 years at transplant

  and/or

- patients with a Haematopoietic Cell Transplantation Co-Morbidity Index *(*HCT-CI) score >2 [according to Sorror et al., Blood. 2005;106(8):2912-9]

2. Availability of an HLA-identical sibling donor (MRD) or HLA-identical unrelated donor (MUD). Donor selection based on molecular high-resolution typing (four digits) of class II alleles of the DRB1 and DQB1 gene loci and molecular (at least) low-resolution typing (two digits) of class I alleles (i.e., antigens) of the HLA- A, B, and C gene loci. In case no class I and class II completely identical donor (10 out of 10 gene loci) could be identified, one antigen disparity (class I) and/or one allele disparity (class II) between patient and donor was acceptable. Conversely, disparity of two antigens (irrespective of the involved gene loci) could not be accepted. These definitions for the required degree of histocompatibility applied to the selection of related as well as unrelated donors.
3. Adult patients of both genders, 18 – 70 years of age
4. Karnofsky Index ≥ 60%
5. Written informed consent
6. Men capable of reproduction and women of childbearing potential had to be willing to consent to using a highly effective method of birth control such as condoms, implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomised partner while on treatment and for at least 6 months thereafter.

Exclusion criteria:

1. Patients with acute promyelocytic leukaemia with t(15;17)(q22;q12) and in first complete remission (CR1)

Applicable in France only:

Patients with the following conditions were excluded from treatment within this protocol

- *patients with cytogenetic favourable acute myeloid leukaemia (low risk' AML) and in CR1, who do not present unfavourable clinical or disease features like secondary or therapy related AML or insufficient response to AML induction therapy*
- *MDS patients with International Prognostic Scoring System (IPSS) low risk' or intermediate I risk' at study entry, who did not present unfavourable clinical features during disease history like refractory severe thrombocytopenia with severe bleeding complications, life-threatening infectious complications due to severe neutropenia and/or very high red blood cell transfusion requirement and related complications'*

2. Patients considered contra-indicated for allogeneic haematopoietic stem cell transplantation (HSCT) due to severe concomitant illness (within three weeks prior to scheduled Day -6):
   - patients with severe renal impairment like patients on dialysis or prior renal transplantation or S-creatinine >3.0 x upper limit of normal (ULN) or calculated creatinine-clearance <60 mL/min
   - patients with severe pulmonary impairment, diffusing capacity of the lung for carbon monoxide (DLCO)/or forced expiratory volume (FEV)1 <50% or severe dyspnoea at rest or requiring oxygen supply
   - patients with severe cardiac impairment diagnosed by electrocardiogram and left ventricular ejection fraction (LVEF) <40%
   - patients with severe hepatic impairment indicated by hyperbilirubinaemia >3 x ULN or alanine aminotransferase (ALT/GPT) / aspartate aminotransferase (AST/GOT) >5 x ULN

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	3. Active malignant involvement of the central nervous system (CNS) 4. Human immunodeficiency virus (HIV)-positivity, active non-controlled infectious disease under treatment (no decrease of C-reactive protein [CRP] or procalcitonin [PCT]) including active viral liver infection 5. Previous allogeneic HSCT 6. Pleural effusion or ascites >1.0 L 7. Pregnancy or lactation 8. Known hypersensitivity to Treosulfan, Busulfan and/or related ingredients 9. Participation in another experimental drug trial within four weeks prior to Day –6 of the protocol 10. Non-cooperative behaviour or non-compliance 11. Psychiatric diseases or conditions that might compromise the ability to give informed consent
Test products, dose and mode of administration, batch number:	Treosulfan intravenously (IV): 14 g/m²/day (1 x 14 g/m²/d) Day -6 to -4 Batch nos.: C100094F; C100094F / C100093I; C100094F / M80306AC; I90002A; I90002A / I90001A; I90002B; I90002B / I90001B; I90002C; I90002C / I90001C; M80310AB; M80310AB / M80306AC; M81031ADI; M81031ADI / M80306AJI; M81031AEPL; M81031AEPL / M81031AEPL; M81031AEPL / M81031AFPL
Duration of treatment:	Patients within the test group were treated on three consecutive days (Day -6 to Day -4) with Treosulfan, while patients in the reference group were treated on two consecutive days (Day -4 to Day -3) with Busulfan. Patients within both treatment groups received the following mandatory non-investigational products: Fludarabine i.v. 30 mg/m²/day IV Day -6 to -2 Ciclosporin-A 5 mg/kg/day oral (PO) Day -1 until Day +100 (level adapted, treatment started IV) Methotrexate (MTX) 15 mg/m² IV Day +1 10 mg/m² IV Day +3, +6 Ca-Folinate 15 mg/m² IV Day +1 (6 hours after MTX) 10 mg/m² IV Day +3, +6 ATG-S-Fresenius 10 mg/kg IV Day -4, -3, -2 (in case of MUD only) ***Applicable in France only:*** *ATG-Thymoglobulin 2.5 mg/kg IV Day -2, -1 (in case of MUD only)*
Reference therapy, dose and mode of administration, batch number:	Busulfan IV: 3.2 mg/kg/d (4 x 0.8 mg/kg/d) Day -4 to -3 Batch nos.: 013018B1; 013019B2; 025212B1; 345142B; 345142B1; 345142B2; 345143B2; 599214B; 599214B1; 599215B; 599215B1; 599216B1; 599218B1; 797783B1; 852752B1; 859739B1; P00001; P00003
Criteria for evaluation:	
Efficacy:	**Event-free survival (EFS)** within one year after transplantation was measured from time of start of HSCT (= Day 0) to time of event. Events were defined as relapse of disease, graft failure, or death (whatever occurred first). **Relapse incidence (RI)** was defined as the probability of having a relapse. Patients were considered experiencing an event when they relapsed. Death without relapse and graft failures were competing risks. Patients alive with no history of relapse were censored at time of last clinical examination of disease status.

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	Overall survival (OS) was defined as the probability of survival irrespective of disease status at any point in time. **Non-relapse mortality (NRM)** was defined as the probability of dying in the absence of persisting disease or previous occurrence of relapse or graft failures **Neutrophil (PMN) engraftment** was to be documented by specifying the first of three consecutive days with absolute neutrophilic granulocyte count >0.5 x 10^9 /L in peripheral blood. **Leukocyte (WBC) engraftment** was to be documented by specifying the first of three consecutive days with total white blood cell count >1 x 10^9 /L in peripheral blood. **Platelet (PLT) engraftment** was to be documented by specifying the first of three consecutive days with platelets >20 x 10^9 /L and >50 x 10^9 /L in the absence of platelet transfusion. **Chimerism** analysis was to be performed on a bone marrow sample of the recipient on Day +28. Peripheral blood might have been used on Day +100. Based on these examinations, complete donor-type chimerism was given if a donor to patient ratio of >=95% was detected. Cumulative incidence and severity of **acute and chronic GvHD** was documented in both treatment groups. Grading of acute (Day 0 until Day +100) and chronic (Day 101 until end of total follow-up at one year after transplantation) GvHD was done according to standard criteria.
Safety:	Assessment of **NRM** as described in Section 'Efficacy' The **cumulative incidence of transplantation related mortality (TRM)** was evaluated up to Day +100 and one year after transplantation. All deaths occurring due to one of the following main causes were considered as transplantation related: • GvHD, • cardiac toxicity, • pulmonary toxicity, • interstitial pneumonitis, • haemorrhage, • Veno-occlusive disease (VOD), • skin toxicity, • Epstein-Barr virus (EBV) proliferative disease, • renal failure, • gastrointestinal toxicity, • rejection/poor graft function, • central nervous system toxicity, • multiple organ failure, • infections (bacterial, viral fungal, parasitic, unknown) or • other HSCT related causes. Cumulative incidence and severity of **acute and chronic GvHD** were documented in both treatment groups. **Adverse events** were documented based on CTCAE v3.0 issued by the National Cancer Institue (NCI). Special attention was given to the frequency of **mucositis/stomatitis** with CTCAE Grade III/IV until Day +28.
Statistical methods:	All data recorded on the Case Report Forms (CRFs) describing the sample, the efficacy and the safety were listed. Descriptive statistics provides frequencies and percentages for categorical data. Continuous data were summarised with number of patients with non-missing observations (N), with number of missing observations (N_{miss}), arithmetic mean, standard deviation, minimum (Min), median, maximum (Max), 25% percentile (Q1) and 75% percentile (Q3). Ordinal data were summarised with Min, Q1, median, Q3, and Max. Chi-square tests were used to compare percentages in a two-by-two contingency table, replaced by Fisher´s exact test if the expected frequency in at least one cell of the associated table was less than five.

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Stratified two-by-two contingency tables were analysed using Cochran-Mantel-Haenszel tests.
Ordinal variables were compared by using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with small number of categories. Any shift in location of quantitative variables between study groups were performed with Wilcoxon-Mann-Whitney tests as well.

The probability of event over time were estimated by Kaplan-Meier methods, when merely non-informative censoring occurred. Log-rank-tests were provided for statistical comparison of this data between treatment arms. Cox proportional hazards models served as a multivariable extension for adjusting the treatment effects for potentially prognostic factors.
In case of competing risks, cumulative incidence and conditional probability functions were used.
Cumulative incidence curves in the presence of competing risks were statistically compared by using the Test of Gray while the Test of Pepe-Mori was applied for conditional cumulative incidence curves.

The following hypothesis system was subject to confirmatory statistical analysis:

Null Hypothesis $HR >= \Theta_0$ vs. Alternative Hypothesis $HR < \Theta_0$,

where HR denoted the ratio of the hazards of events in the test group divided by the hazard of events within the reference group and Θ_0 denoted the pre-specified non-inferiority margin of $\theta_o = 1.3$.

For confirmatory analysis a two-sided 95% confidence interval (C.I.) with confidence coefficient $(1-2\alpha)$ for the difference between EFS was provided. The Treosulfan regimen was deemed to be not less effective than Busulfan regimen if the lower limit of this C.I. was greater than the pre-specified non-inferiority margin of roughly -10%. Statistical significance was claimed if the resulting p-value was less than the pre-specified experiment-wise significance level of 0.025.

If significant non-inferiority was shown, superiority as to the primary endpoint was tested and in addition, the first secondary safety objective was subjected to confirmatory analysis.

Interim analyses:

In order to stop the trial as soon as the question of non-inferiority was answered, a group-sequential approach was implemented with three confirmatory interim analyses and one final look. Interim analyses were to be performed after documentation of at least 90 events in at least 230 patients, 145 events (or latest with 345 patients) and 190 events (or latest with 440 patients) qualifying for per protocol set.

Safety monitoring:

An independent safety monitoring committee was implemented to supervise the trial with respect to efficacy and any potentially relevant treatment-specific differences in TRM and serious adverse events (SAEs).

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SUMMARY OF RESULTS

Based on the results of the first scheduled interim analysis of 279 enrolled patients, the study was amended (Amendment No. 03) following recommendations of the Data Monitoring Committee. Results of the first 330 patients included prior to implementation of Amendment No. 03 are reported in this clinical study report.

As the initially planned power of the study was not reached with 330 out of 545 planned patients included in this analysis, the conclusions drawn in this clinical study report are merely descriptive.

EFFICACY RESULTS:

Disposition of patients

	Busulfan	Treosulfan	Total
Patients Randomised	159 (100%)	171 (100%)	330 (100%)
Patients in Full Analysis Set	152 (95.6%)	168 (98.2%)	320 (97%)
Patients in Safety Analysis Set	152 (95.6%)	168 (98.2%)	320 (97%)
Patients in Per Protocol Set	140 (88.1%)	165 (96.5%)	305 (92.4%)

Selected patient characteristics (Full Analysis Set)

Number of patients	152 (100.0%)	168 (100.0%)	320 (100.0%)
Patient's Age (years)			
Median (Q1, Q3)	58.0 (54.0, 63.0)	59.0 (53.0, 63.0)	58.0 (54.0, 63.0)
Patients HCT-CI Score			
Median (Q1, Q3)	3.0 (2.0, 5.0)	3.0 (1.0, 4.0)	3.0 (2.0, 5.0)
Diagnosis			
AML	109 (71.7%)	130 (77.4%)	239 (74.7%)
MDS	43 (28.3%)	38 (22.6%)	81 (25.3%)
Donor Type			
MRD	32 (21.1%)	45 (26.8%)	77 (24.1%)
MUD	120 (78.9%)	123 (73.2%)	243 (75.9%)
Remission status at study entry			
CR1	80 (73.4%)	99 (76%2%)	179 (74.9%)
>CR1	29 (26.6%)	31 (23.8%)	60 (25.1%)

Both treatment groups were comparable concerning demographics and baseline characteristics.

Summary of efficacy results (Full Analysis Set)

	Busulfan	Treosulfan	p-Value*
Event-free survival [%] (95% C.I.)			
12 months	67.5 (59.3, 74.3)	62.1 (54.3, 69.0)	0 2927
24 months	56.9 (48.2, 64.7)	51.2 (42.8, 59.0)	0 1643
Overall survival [%] (95% C.I.)			
12 months	74.3 (66.5, 80.5)	68.0 (60.3, 74.5)	0 2211
24 months	64.2 (55.7, 71.6)	60.2 (51.8, 67.6)	0.4118
Relapse incidence [%] (95% C.I.)			
12 months	17.5 (11.3, 23.7)	17.4 (11.6, 23.3)	0 9151
24 months	22.1 (15.2, 29.1)	23.5 (16.6, 30.3)	0.6107
Non-relapse mortality [%] (95% C.I.)			
12 months	14.5 (8.9, 20.1)	19.2 (13.2, 25.2)	0 3224
24 months	20.2 (13.5, 27.0)	24.0 (17.1, 30.8)	0 5591
Transplant related mortality [%](95% C.I.)			
Day +100	5.3 (2.7, 10.4)	10.2 (6.4, 15.9)	0.0385
12 months	14.3 (9.6, 21.1)	19.1 (13.8, 26.1)	0 1758
Transplant related mortality [%] (95% C.I.)			
Day +100 'infection related only'	4.0 (1.8, 8.7)	7.9 (4.7, 13.3)	0.0630
12 months 'infection related only'	11.2 (7.0, 17.6)	17.1 (12.0, 23.9)	0.0637

* p-value for testing difference of Treosulfan compared to Busulfan

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- Exploratory subgroup analyses (MUD vs. MRD; risk group I vs. II; donor type in combination with risk group I vs. II; AML vs. MDS; <50 years vs. >=50 years; HCT-CI score <=2 vs. >2, AML CR1 vs. >CR1; AML risk group I vs. II; untreated vs. treated MDS and MDS risk group I vs. II) regarding engraftment revealed that MRD patients of the Treosulfan treatment group had a significantly earlier median engraftment of granulocytes than patients of the Busulfan treatment group. Patients with MUD as well as patients aged >=50years receiving Busulfan had a significantly earlier median engraftment of leukocytes and platelets than patients of the Treosulfan treatment group.

Results were comparable for the Per Protocol Set.

SAFETY RESULTS:

The most relevant results of the safety analysis of the first 330 patients are given below:

Summary of safety evaluation AEs, SAEs (Safety Analysis Set)

	Busulfan	Treosulfan	Total
Number of patients	152 (100.0%)	168 (100%)	320 (100.0%)
Patients with AEs of any CTCAE Grade	146 (96.1%)	168 (100.0%)	314 (98.1%)
Patients with AEs of at least CTCAE Grade III	96 (63 2%)	122 (72.6%)	218 (68.1%)
Patients with drug related AEs of at least CTCAE Grade III	61 (40 1%)	67 (39.9%)	128 (40.0%)
Patients with Infection of any CTCAE Grade	75 (49 3%)	107 (63.7%)	182 (56.9%)
Patients with Infections of at least CTCAE Grade III	55 (36 2%)	92 (54.8%)	147 (45.9%)
Patients with at least one SAE	9 (5.9%)	19 (11.3%)	28 (8.8%)
Patients with at least one SAE Infection	3 (2.0%)	11 (6.5%)	14 (4.4%)

- Despite minor differences between the treatment groups regarding single CTCAE Categories, the overall AE experience in the study was comparable between the treatment groups apart from more infectious complications and a slightly higher incidence of severe AEs (>=CTCAE Grade III) in the Treosulfan treatment group. AEs that occurred most often belong to CTCAE Category gastrointestinal, pain, metabolic/laboratory, infection, constitutional symptoms, cardiac general, dermatology/skin, lymphatics, neurology, and haemorrhage/bleeding.
- A slightly higher frequency of SAEs, most notably infections, was noted for the Treosulfan treatment group compared to the Busulfan treatment group.

Overview and cause of deaths until end of follow-up (Safety Analysis Set)

	Busulfan	Treosulfan	Total
Number of patients	152 (100.0%)	168 (100.0%)	320 (100.0%)
alive	112 (73.7%)	115 (68.5%)	227 (70.9%)
death	40 (26.3%)	53 (31.5%)	93 (29.1%)
Cause of death			
Relapse	17 (11.2%)	18 (10.7%)	35 (10.9%)
Transplantation related cause	22 (14.5%)	31 (18.5%)	53 (16.6%)
Secondary malignancy	1 (0.7%)	0 (0%)	1 (0.3%)
Other	0 (0%)	4 (2.4%)	4 (1.3%)

- Both treatment groups were comparable regarding the frequency of relapse related deaths.
- During the study, more transplantation related deaths occurred in the Treosulfan treatment group compared to the Busulfan treatment group (refer also to efficacy results).

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Summary of incidences of CTCAE Grade III/IV mucositis/stomatitis, VOD, seizures and hyperbilirubinaemia

	Busulfan	Treosulfan	p-Value*
Number of patients	152 (100%)	168 (100%)	
Patients with Mucositis/Stomatitis	26 (17.1%)	18 (10.7%)	0.0704
Patients with VOD	1 (0.7%)	1 (0.6%)	0.8236
Patients with Seizures	1 (0.7%)	0 (0.0%)	0.2986
Patients with Hyperbilirubinaemia	11 (7.2%)	21 (12.5%)	0.0882

* adjusted p-value for testing difference

Summary of cumulative incidence of acute and chronic GvHD (Safety Analysis Set)

	Busulfan	Treosulfan	p-Value*
Acute GvHD grade III - IV on Day +100 [%] (95% C.I.)	9.2 (4.6, 13.8)	14.3 (9.0, 19.6)	0.1469
Chronic GvHD (extensive) on Month 12 [%] (95% C.I.)	24.2 (16.6, 31.8)	24.3 (17.0, 31.6)	0.9418

* test of Gray

- No significant differences between the treatment groups were noted regarding acute GvHD, chronic GvHD, VOD, mucositis/stomatitis, seizures, hyperbilirubinemia, and other routine laboratory examinations.

From the observations described above it was concluded, that the Treosulfan-based conditioning regimen was more intense than the Busulfan-based regimen used as comparator in this study.

Consequently, a longer duration of cytopenia, more frequent and more severe early complications, namely infections, and a higher TRM were observed in the Treosulfan treatment group.

CONCLUSION:

Following the first confirmatory interim analysis of 279 patients the current study was substantially amended regarding the dose and schedule of the Treosulfan regimen (Amendment No. 03). Unfavourable findings as to increased infectious complications after Treosulfan-based conditioning treatment, were considered to be a consequence of an imbalanced dosing between the Treosulfan and the Busulfan based regimen.

The current final analysis of 330 patients enrolled before implementation of Amendment No. 03 confirmed the unfavourable findings of the first confirmatory interim analysis and the subsequent decision

- to reduce the Treosulfan dose in the test arm from 3 x 14 g/m² Treosulfan to 3 x 10 g/m² and
- to start administration of test- and reference drug on the same day (Day -4 prior to allogeneic HSCT).

in order to render the Treosulfan regimen more similar to the reduced-intensity Busulfan regimen.

With a total number of 330 out of 545 planned patients included at the timepoint of this analysis, however, the primary objective of the study (non-inferiority of Treosulfan-based conditioning compared to Busulfan-based conditioning regarding EFS at 12 months after transplantation) could not be demonstrated. The conditional probability to show significant non-inferiority with regard to EFS with the planned final number of patients was very low, so that patient randomisation stopped in September 2011 by a DMC recommendation and was re-started only after modification of the Treosulfan regimen.

Implementation of Amendment No. 03 required a new sample size calculation to assess non-inferiority of the modified Treosulfan-based conditioning regimen. Due to the EU-orphan drug status of Treosulfan, these substantial changes were addressed to the EMA/CHMP/SAWP for protocol assistance. In their Final Advice Letter dated 17-Jan-2013, the European authority confirmed the proposed protocol amendment. Patient enrollment in the amended protocol MC-FludT.14/L re-started in June 2013.

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