Clinical trial results:
Allogenic stem cell transplantation in children and adolescents with acute lymphoblastic leukaemia

Summary

EudraCT number	2005-005106-23
Trial protocol	AT IT
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	12 April 2024
First version publication date	12 April 2024

Trial information

Trial identification

Sponsor protocol code	ALLSCT06BFMi

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01423500
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St. Anna Kinderkrebsforschung GmbH
Sponsor organisation address	Zimmermannplatz 10, Vienna , Austria, 1090
Public contact	Univ.Prof. Dr. Ruth Ladenstein, St. Anna Kinderkrebsforschung GmbH, +43 1 40470 4750, ruth.ladenstein@ccri.at
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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	21 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

*To evaluate whether HSCT from matched family or unrelated donors (MD) is equivalent to the HSCT from matched sibling donors (MSD)
*To evaluate the efficacy of HSCT from mismatched family or unrelated donors (MMD) as compared to HSCT from MSD/MD.
*To determine whether therapy has been carried out according to the main HSCT protocol recommendations. The standardisation of the treatment options during HSCT from different donor types aims at the achievement of an optimal comparison of survival after HSCT with survival after chemotherapy only.
*To prospectively evaluate and compare the incidence of acute and chronic GvHD after HSCT from MSD, from MD and from MMD.

Protection of trial subjects:

Detailed supportive care measures have been specified in the trial protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Czechia: 34
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	France: 71
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Netherlands: 50
Country: Number of subjects enrolled	Poland: 131
Country: Number of subjects enrolled	Slovakia: 17
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Turkey: 46
Worldwide total number of subjects	450
EEA total number of subjects	390

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)	19
Children (2-11 years)	276
Adolescents (12-17 years)	146
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment in the period from 21.02.2007 until 9 September 2011 in 12 countries.

Pre-assignment

Screening details:

Principal inclusion criteria:
- age at time of initial diagnosis or relapse ≤18 years (until 19th birthday)
- indication for hematopoietic stem cell transplantation (HSCT)
- complete remission
- no pregnancy
- no secondary malignancy
- no previous HSCT
- written consent

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Matched Sibling Donor (MSD)

Arm description:

HSCT with HLA-genotypically identical sibling donor or a 10 out of 10 (high resolution – 4 digits per allel) matched sibling donor if the parental haplotypes are unknown.

Assigned Interventions: TBI/VP16 based conditioning regimen for patients older than 24 months -
VP16 at a dose of 60mg/kg/d on day -3;
Total body irradiation (TBI) at a dose of 2x2Gy/day for 3 days (total 12Gy in 6 fractions) on days -6, -5, -4.
Patients younger than 24 months receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg).

Patients with ALL and translocation t(4;11) who receive stem cells from a MSD or MD and infants with indication for allogeneic HSCT (according to the INTERFANT-protocol) are prepared
for HSCT with a specific triple-drug-conditioning: Bu (BW adjusted)/Cyclo (60 mg/kg)/MEL (140mg/m2).

Arm type	Active comparator
Investigational medicinal product name	Etoposid/VP16
Investigational medicinal product code	
Other name	Etopophos
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide is administered as a single infusion over 4 hours. The dosage is 60mg/kg BW (maximum 1800mg/m2 BS, absolute dose 3,6 g max.) or 40mg/kg BW (maximum 1200mg/m2 BS, absolute dose 2,4 g max.) respectively, depending on the conditioning regimen. The infusion is to be performed in accordance with the guidelines of the transplantation centre. VP16 is administered on day -3 in patients with TBI or on day -4 before allogeneic HSCT in those without TBI. If etoposide phosphate is used, the dosage is adapted to the aliquot etoposide according to the recommendations of the pharmaceutical drug description.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion

Routes of administration	Intravenous use

Dosage and administration details:

Melphalan is given intravenous once at a dose of 140 mg/m2. Melphalan is chemically instable in solution and should be given as soon as possible (within 1 hour) after being dissolved. It can only be diluted with normal saline and may not come in contact with glucose. Parenteral nutrition containing amino acids has to be stopped 2 hours before administration of Melphalan to prevent competition with cellular uptake of the drug.

Investigational medicinal product name	Cyclophosphamid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total dose for Cyclophosphamide is 120 mg/kg BW. It is administered in 2 single doses of 60mg/kg given over 1 hour i.v. on 2 consecutive days (-3 and -2). Between the last BUX application and the infusion of CYCLO an interval of 24 hours is mandatory.

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	Busilfex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BUX is given at weight-adjusted doses. As i.v. Busulfan is registered as orphan drug and because of its more predictable pharmacology and decreased hepatic toxicity by lack of first-pass effect, only i.v. Busulfan is used in this study. BUX is administered in 16 single doses. The BUX infusions are given over 2 hours in six hours distance on 4 consecutive days. Seizure prophylaxis with Phenytoin is started before Busulfan i.v. application, continued for 2 days after the last dose, and then tapered.

Arm title	Matched Donor (MD)

Arm description:

HSCT with related or unrelated stem cell donors, 10 or 9 out of 10 HLA matches determined by high resolution typing (4 digits per allele) and MMD BM 8/10.
Assigned Interventions: TBI/VP16 based conditioning regimen - VP16 (60mg/kg/d on day -3); Total body irradiation (TBI) (2x2Gy/day over 3 days on day -6, -5, -4); Patients younger than 24 months receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg). ATG is given to both age groups at a dose of 20mg/kg/d on days -3, -2, -1.

Patients with ALL and translocation t(4;11) who receive stem cells from a MSD or MD and infants with indication for allogeneic HSCT (according to the INTERFANT-protocol) are prepared
for HSCT with a specific triple-drug-conditioning: Bu (BW adjusted)/Cyclo (60 mg/kg)/MEL (140mg/m2).

Arm type	Active comparator
Investigational medicinal product name	Etoposid/VP16
Investigational medicinal product code	
Other name	Etopophos
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide is administered as a single infusion over 4 hours. The dosage is 60mg/kg BW (maximum 1800mg/m2 BS, absolute dose 3,6 g max.) or 40mg/kg BW (maximum 1200mg/m2 BS, absolute dose 2,4 g max.) respectively, depending on the conditioning regimen. The infusion is to be performed in accordance with the guidelines of the transplantation centre. VP16 is administered on day -3 in patients with TBI or on day -4 before allogeneic HSCT in those without TBI. If etoposide phosphate is used, the dosage is adapted to the aliquot etoposide according to the recommendations of the pharmaceutical drug description.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Melphalan is given intravenous once at a dose of 140 mg/m2. Melphalan is chemically instable in solution and should be given as soon as possible (within 1 hour) after being dissolved. It can only be diluted with normal saline and may not come in contact with glucose. Parenteral nutrition containing amino acids has to be stopped 2 hours before administration of Melphalan to prevent competition with cellular uptake of the drug.

Investigational medicinal product name	Cyclophosphamid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total dose for Cyclophosphamide is 120 mg/kg BW. It is administered in 2 single doses of 60mg/kg given over 1 hour i.v. on 2 consecutive days (-3 and -2). Between the last BUX application and the infusion of CYCLO an interval of 24 hours is mandatory.

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	Busilfex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BUX is given at weight-adjusted doses. As i.v. Busulfan is registered as orphan drug and because of its more predictable pharmacology and decreased hepatic toxicity by lack of first-pass effect, only i.v. Busulfan is used in this study. BUX is administered in 16 single doses. The BUX infusions are given over 2 hours in six hours distance on 4 consecutive days. Seizure prophylaxis with Phenytoin is started before Busulfan i.v. application, continued for 2 days after the last dose, and then tapered.

Investigational medicinal product name	ATG Fresenius
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ATG-Fresenius S is an anti-human T-lymphocyte immunoserum which is obtained from rabbits immunised with human T-lymphoblasts of the Jurkat cell-line. ATG-Fresenius S is administered at a dose of 20 mg/kg BW on three consecutive days (day –3 until day –1). The infusion is hypotonic and may only be dissolved with normal saline. Furthermore, Heparin may not be administered as mixed infusion or via the same vascular access, as this can lead to a shift in the pH-value. The infusion may be given over 4 hours, and a premedication with steroids (max. 2mg/kg BW) is recommended. The respective emergency medicines need to be ready for immediate intervention, and frequent checks of the vital parameters are required.

Arm title	Mismatched Donor (MMD)

Arm description:

Patients with a MMD receive stem cells extracted from bone marrow, cord blood or peripheral blood from a haploidentical donor (parent) or from a non-related donor with a match less or equal to 8/10.

Assigned Interventions for patients with a BM 8/10 donor and older than 24 months: TBI/VP16 based conditioning regimen - VP16 (60mg/kg/d on day -3); Total body irradiation (TBI) (2x2Gy/day over 3 days on day -6, -5, -4); Patients younger than 24 months with a BM 8/10 donor receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg). They all receive ATG (20mg/kg/d on day -3,-2,-1).

Assigned Interventions for patients with Haploidentical and cord blood HSCT: Fludarabine (30mg/m²/d on day -9 to -5), OKT3 (0,0125-0,1mg/kg on day -9 to 0), ATG fresenius (20mg/kg/d on day -3,-2,-1), Treosulfan (14g/m²/d on day -7 to -5) and Thiotepa (2x5mg/kg/d on day -4).

Arm type	Active comparator

Investigational medicinal product name	Etoposid/VP16
Investigational medicinal product code	
Other name	Etopophos
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide is administered as a single infusion over 4 hours. The dosage is 60mg/kg BW (maximum 1800mg/m2 BS, absolute dose 3,6 g max.) or 40mg/kg BW (maximum 1200mg/m2 BS, absolute dose 2,4 g max.) respectively, depending on the conditioning regimen. The infusion is to be performed in accordance with the guidelines of the transplantation centre. VP16 is administered on day -3 in patients with TBI or on day -4 before allogeneic HSCT in those without TBI. If etoposide phosphate is used, the dosage is adapted to the aliquot etoposide according to the recommendations of the pharmaceutical drug description.

Investigational medicinal product name	ATG Fresenius
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ATG-Fresenius S is an anti-human T-lymphocyte immunoserum which is obtained from rabbits immunised with human T-lymphoblasts of the Jurkat cell-line. ATG-Fresenius S is administered at a dose of 20 mg/kg BW on three consecutive days (day –3 until day –1). The infusion is hypotonic and may only be dissolved with normal saline. Furthermore, Heparin may not be administered as mixed infusion or via the same vascular access, as this can lead to a shift in the pH-value. The infusion may be given over 4 hours, and a premedication with steroids (max. 2mg/kg BW) is recommended. The respective emergency medicines need to be ready for immediate intervention, and frequent checks of the vital parameters are required.

Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	Busilfex®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BUX is given at weight-adjusted doses. As i.v. Busulfan is registered as orphan drug and because of its more predictable pharmacology and decreased hepatic toxicity by lack of first-pass effect, only i.v. Busulfan is used in this study. BUX is administered in 16 single doses. The BUX infusions are given over 2 hours in six hours distance on 4 consecutive days. Seizure prophylaxis with Phenytoin is started before Busulfan i.v. application, continued for 2 days after the last dose, and then tapered.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients with Mismatched Family Donor (MMFD) HSCT receive Fludarabine i.v. as single dose of 40mg/m2 over 30 minutes at noon for 4 consecutive days. The total dose is 160 mg/m2.

Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treosulfan is an alkylating agents with a half-life of 88 minutes. It is administered at a dose of 14g/m²/d for 3 days (total dose 42g/m²) and for babies < 9kg BW 12g/m²/d for 3 days (total dose 36g/m²). The infusion is given over 1 hour. The solution remains stable at room temperature for 4 days.

Investigational medicinal product name	Orthoclone OKT3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

OKT3 is a murine monoclonal antibody with specific affect against a glycoprotein of the CD-3 complex on human T-lymphocytes. T

Investigational medicinal product name	Thiotepa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Thiopeta is an alkylating agents with cytolytic and radiomimetic effects. It is administered at a dose of 2x5mg/kg for 1 day (total dose 10mg/kg) and for babies < 9 kg BW 2x3,5mg/kg for 1 day (total dose 7mg/kg).

Investigational medicinal product name	Cyclophosphamid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total dose for Cyclophosphamide is 120 mg/kg BW. It is administered in 2 single doses of 60mg/kg given over 1 hour i.v. on 2 consecutive days (-3 and -2). Between the last BUX application and the infusion of CYCLO an interval of 24 hours is mandatory.

Number of subjects in period 1	Matched Sibling Donor (MSD)	Matched Donor (MD)	Mismatched Donor (MMD)
Started	150	235	65
Completed	150	235	65

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	450	450	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	19	19	
Children (2-11 years)	276	276	
Adolescents (>=12 years)	155	155	
Gender categorical Units: Subjects			
Female	140	140	
Male	310	310	

Subject analysis sets	
Subject analysis set title	MSD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MSD (matched sibling donor), having indication for HSCT from MD or MMD

Subject analysis set title	MD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MD (matched donor), having indication for HSCT from MD or MMD

Subject analysis set title	MMD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MMD (mismatched donor), having indication for HSCT from MMD

Subject analysis set title	MSD/MD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MSD or MD (matched sibling donor or matched donor), having indication for HSCT from MMD

Reporting group values	MSD	MD	MMD
Number of subjects	128	217	36
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	4	11	1
Children (2-11 years)	77	133	24
Adolescents (>=12 years)	47	73	11

Gender categorical Units: Subjects			
Female	45	60	8
Male	83	157	28

Reporting group values	MSD/MD		
Number of subjects	187		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7		
Children (2-11 years)	112		
Adolescents (>=12 years)	68		
Gender categorical Units: Subjects			
Female	55		
Male	132		

End points

End points reporting groups

Reporting group title	Matched Sibling Donor (MSD)

Reporting group description:

HSCT with HLA-genotypically identical sibling donor or a 10 out of 10 (high resolution – 4 digits per allel) matched sibling donor if the parental haplotypes are unknown.

Assigned Interventions: TBI/VP16 based conditioning regimen for patients older than 24 months - VP16 at a dose of 60mg/kg/d on day -3;
Total body irradiation (TBI) at a dose of 2x2Gy/day for 3 days (total 12Gy in 6 fractions) on days -6, -5, -4.
Patients younger than 24 months receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg).

Patients with ALL and translocation t(4;11) who receive stem cells from a MSD or MD and infants with indication for allogeneic HSCT (according to the INTERFANT-protocol) are prepared for HSCT with a specific triple-drug-conditioning: Bu (BW adjusted)/Cyclo (60 mg/kg)/MEL (140mg/m2).

Reporting group title	Matched Donor (MD)

Reporting group description:

HSCT with related or unrelated stem cell donors, 10 or 9 out of 10 HLA matches determined by high resolution typing (4 digits per allele) and MMD BM 8/10.
Assigned Interventions: TBI/VP16 based conditioning regimen - VP16 (60mg/kg/d on day -3); Total body irradiation (TBI) (2x2Gy/day over 3 days on day -6, -5, -4); Patients younger than 24 months receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg). ATG is given to both age groups at a dose of 20mg/kg/d on days -3, -2, -1.

Patients with ALL and translocation t(4;11) who receive stem cells from a MSD or MD and infants with indication for allogeneic HSCT (according to the INTERFANT-protocol) are prepared for HSCT with a specific triple-drug-conditioning: Bu (BW adjusted)/Cyclo (60 mg/kg)/MEL (140mg/m2).

Reporting group title	Mismatched Donor (MMD)

Reporting group description:

Patients with a MMD receive stem cells extracted from bone marrow, cord blood or peripheral blood from a haploidentical donor (parent) or from a non-related donor with a match less or equal to 8/10.

Assigned Interventions for patients with a BM 8/10 donor and older than 24 months: TBI/VP16 based conditioning regimen - VP16 (60mg/kg/d on day -3); Total body irradiation (TBI) (2x2Gy/day over 3 days on day -6, -5, -4); Patients younger than 24 months with a BM 8/10 donor receive Bu (BW adjusted)/VP16 (40mg/kg)/Cyclo (60 mg/kg). They all receive ATG (20mg/kg/d on day -3,-2,-1).

Assigned Interventions for patients with Haploidentical and cord blood HSCT: Fludarabine (30mg/m²/d on day -9 to -5), OKT3 (0,0125-0,1mg/kg on day -9 to 0), ATG fresenius (20mg/kg/d on day -3,-2,-1), Treosulfan (14g/m²/d on day -7 to -5) and Thiotepa (2x5mg/kg/d on day -4).

Subject analysis set title	MSD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MSD (matched sibling donor), having indication for HSCT from MD or MMD

Subject analysis set title	MD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MD (matched donor), having indication for HSCT from MD or MMD

Subject analysis set title	MMD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MMD (mismatched donor), having indication for HSCT from MMD

Subject analysis set title	MSD/MD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients with MSD or MD (matched sibling donor or matched donor), having indication for HSCT from MMD

Primary: EFS (Event free survival)

End point title	EFS (Event free survival)

End point description:

Event are defined as: leukemic relapse at any site, secondary malignancy, death of any cause.

End point type	Primary

End point timeframe:

Starting point of the analysis: date of HSCT. End point of the analysis is the date of event or the last available follow up date.

End point values	MSD	MD	MMD	MSD/MD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	128	217	36	187
Units: %				
number (not applicable)	128	217	36	187

Statistical analyses

Statistical analysis title	EFS (study question 1)

Statistical analysis description:

The null hypothesis was that HSCT from MD was inferior to SCT from MSD.
The calculation is done by a one-sided confidence interval for the difference of the Kaplan-Meier estimates of 4-year Event-free Survival (EFS) between both subgroups.
Only patients with indication for MD or MMD were included into this analysis.

Comparison groups	MSD v MD
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference of KM estimates of 4y-EFS
Point estimate	0.04
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.14

Notes:

[1] - One sided confidence interval of the difference of the Kaplan-Meier (KM) estimates of the 4-years EFS of both subgroups (MSD and MD) is calculated.
Hematopoietic stem cell transplantation from a matched donor (MD) is considered non-inferior to that from a matched sibling donor (MSD) if the pEFS of patients from MD does not fall below that of patients from MSD by more than 0.15.

Statistical analysis title	EFS (study question 2)

Statistical analysis description:

Kaplan-Meier method was used to estimate EFS, and Log Rank test to compare both subgroups.
Null hypothesis: The EFS of patients with MMS does not differ from that of patients with MSD/MD.
Only patients with indication for MMD were included into this analysis.

Comparison groups	MMD v MSD/MD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Logrank

Secondary: Occurrence of acute Graft-versus-Host-Disease (GvHD)

End point title	Occurrence of acute Graft-versus-Host-Disease (GvHD)

End point description:

The incidence of acute GvHD equals the proportion of patients with at least one episode of acute GvHD > grade I up to Day+100 after HSCT.

End point type	Secondary

End point timeframe:

The period up to day +100 after HSCT.

End point values	MSD	MD	MMD	MSD/MD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	128	217	36	187
Units: %				
number (not applicable)	128	217	36	187

Statistical analyses

Statistical analysis title	Comparison of acute GVHD grade > 1 - MSD vs MD
Comparison groups	MSD v MD
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.562
Method	Fisher exact

Statistical analysis title	Comparison of acute GVHD grade > 1 - MSD/MD vs MMD
Comparison groups	MMD v MSD/MD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349
Method	Fisher exact

Secondary: Occurrence of chronic Graft-versus-Host-Disease (GvHD)

End point title	Occurrence of chronic Graft-versus-Host-Disease (GvHD)

End point description:

The incidence of GvHD equals the proportion of patients with at least one episode of chronic GvHD (limited or extended) up to a period of five years after HSCT.
These endpoint was estimated using the approach of Prentice and Kalbfleisch, allowing for competing risks, which were death in remission and relapse.

End point type	Secondary

End point timeframe:

Time period between the HSCT and end of 5-year Follow-up.

End point values	MSD	MD	MMD	MSD/MD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	128	217	36	187
Units: %				
number (not applicable)	128	217	36	187

Statistical analyses

Statistical analysis title	Comparison of chronic GVHD - MSD vs MD
Comparison groups	MSD v MD
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Gray

Statistical analysis title	Comparison of chronic GVHD - MSD and MD vs MMD
Comparison groups	MMD v MSD/MD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.979
Method	Gray

Secondary: OS (Overall survival)

End point title	OS (Overall survival)

End point description:

End point type	Secondary

End point timeframe:

Starting point of the analysis: date of HSCT. End point is the date of death of any cause or the last available follow up date.

End point values	MSD	MD	MMD	MSD/MD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	128	217	36	187
Units: %				
number (not applicable)	128	217	36	187

Statistical analyses

Statistical analysis title	(OS study question 1)

Statistical analysis description:

Kaplan-Meier method was used to estimate OS, and the Log Rank test to compare both subgroups. Only patients with indication for MD and MMD were used for this analysis.

Comparison groups	MSD v MD
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	Logrank

Statistical analysis title	(OS study question 2)

Statistical analysis description:

Kaplan-Meier method was used to estimate OS, and the Log Rank test to compare both subgroups. Only patients with indication for MD and MMD were used for this analysis.

Comparison groups	MMD v MSD/MD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Period from start of conditioning until end of 5-year follow-up

Adverse event reporting additional description:

All adverse events that occur from start of conditioning are reported in the patient's records and according to national standards on adverse event reporting. Those meeting the definition of a serious adverse event must be reported using the Serious Adverse Event (SAE) Report form.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	MSD (matched sibling donors)
Reporting group description: -	
Reporting group title	MD (matched family or unrelated donors)
Reporting group description: -	
Reporting group title	MMD (mismatched donors)
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events have not been reported explicitly, but rather the maximum grade of toxicity for each of the predefined toxicity categories and time intervals.

Serious adverse events	MSD (matched sibling donors)	MD (matched family or unrelated donors)	MMD (mismatched donors)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 150 (7.33%)	21 / 235 (8.94%)	6 / 65 (9.23%)
number of deaths (all causes)	38	71	25
number of deaths resulting from adverse events	4	6	6
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	2 / 150 (1.33%)	5 / 235 (2.13%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	2 / 2	8 / 8	0 / 0
deaths causally related to treatment / all	2 / 2	2 / 4	0 / 0
Nervous system disorders			
Cerebral thrombosis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Coma			

subjects affected / exposed	1 / 150 (0.67%)	0 / 235 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Encephalopathy			
subjects affected / exposed	3 / 150 (2.00%)	0 / 235 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	2 / 2	0 / 0	1 / 1
Nervous system disorder			
subjects affected / exposed	1 / 150 (0.67%)	0 / 235 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Psychiatric symptom			
subjects affected / exposed	2 / 150 (1.33%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Seizure			
subjects affected / exposed	3 / 150 (2.00%)	2 / 235 (0.85%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	2 / 2	1 / 2	0 / 0
Blood and lymphatic system disorders			
Coagulation disorder			
subjects affected / exposed	1 / 150 (0.67%)	4 / 235 (1.70%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	4 / 4	1 / 1
deaths causally related to treatment / all	1 / 1	3 / 4	1 / 1
General disorders and administration site conditions			
Anaphylactic reaction			
subjects affected / exposed	1 / 150 (0.67%)	2 / 235 (0.85%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 2	0 / 0
Skeletal injury			
subjects affected / exposed	2 / 150 (1.33%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	4 / 150 (2.67%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	3 / 4	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	7 / 150 (4.67%)	4 / 235 (1.70%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	7 / 7	4 / 4	0 / 0
deaths causally related to treatment / all	4 / 6	2 / 3	0 / 0
Venoocclusive disease			
subjects affected / exposed	1 / 150 (0.67%)	7 / 235 (2.98%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	7 / 7	1 / 1
deaths causally related to treatment / all	1 / 1	3 / 5	1 / 1
Respiratory, thoracic and mediastinal disorders			
ARDS			
subjects affected / exposed	2 / 150 (1.33%)	5 / 235 (2.13%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	2 / 2	5 / 5	3 / 3
deaths causally related to treatment / all	1 / 2	3 / 4	3 / 3
Alveolar hemorrhage			
subjects affected / exposed	3 / 150 (2.00%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 3	0 / 0	0 / 0
Engraftment syndrome			
subjects affected / exposed	1 / 150 (0.67%)	1 / 235 (0.43%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Respiratory thoracic and mediastinal disorders			
subjects affected / exposed	4 / 150 (2.67%)	7 / 235 (2.98%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	5 / 5	10 / 10	3 / 3
deaths causally related to treatment / all	2 / 4	4 / 7	3 / 3
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			

subjects affected / exposed	3 / 150 (2.00%)	1 / 235 (0.43%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	3 / 3	0 / 1	0 / 0
Renal and urinary disorders			
Acute toxic failure			
subjects affected / exposed	0 / 150 (0.00%)	2 / 235 (0.85%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Hemorrhagic cyctitis			
subjects affected / exposed	1 / 150 (0.67%)	1 / 235 (0.43%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Renal and urinary disorder			
subjects affected / exposed	1 / 150 (0.67%)	2 / 235 (0.85%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 0
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	1 / 150 (0.67%)	0 / 235 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	4 / 150 (2.67%)	14 / 235 (5.96%)	4 / 65 (6.15%)
occurrences causally related to treatment / all	5 / 5	19 / 19	4 / 4
deaths causally related to treatment / all	3 / 4	8 / 13	4 / 4

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	MSD (matched sibling donors)	MD (matched family or unrelated donors)	MMD (mismatched donors)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 150 (0.00%)	0 / 235 (0.00%)	0 / 65 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2009	Extension of recruitment for 2 further years; Definition of HSCT options and stem cell source for patients with a MMD donor; Complement and new conditioning schemes for MMD HSCT; Exclusion of TBI based conditioning for MMD HSCT; Definition of GvHD prophylaxis; Correction of study period; Additional consent for patients reaching 18 years of age during participation in a study,

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31319153