Clinical trial results:
A prospective randomized study comparing rapamune and tacrolimus vs. cyclosporine and methotrexate as immune prophylaxis in allogeneic hematopoietic stem cell transplantation, using HLA-A, -B, -DRB1 identical related or unrelated donors. A Nordic multicenter study.

Summary

EudraCT number	2006-006577-25
Trial protocol	SE FI
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	26 February 2023
First version publication date	26 February 2023

Trial information

Trial identification

Sponsor protocol code	070101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00993343
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Nobels väg 6, Solna, Sweden,
Public contact	Olle Ringdén, Karolinska Institutet, olle.ringden@ki.se
Scientific contact	Olle Ringdén, Karolinska Institutet, olle.ringden@ki.se

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	19 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2015
Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if the immunosuppressive prophylaxis with tacrolimus and sirolimus is better than the established therapy using cyclosporine and methotrexate in preventing graft versus host disease

Protection of trial subjects:

The study protocol was approved by the Ethical Review Boards in Stockholm (DNR 2006/1430-31/3) and Helsinki (#541/2007, DNR 360/E5/07), and the Swedish and Finnish Medical Products Agencies (DNR 151:2007/38987 and KLNR 57/2008, respectively). The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient, or from parents/guardians of patients who were under 18 years of age, before the start of HSCT conditioning treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 200
Country: Number of subjects enrolled	Finland: 15
Worldwide total number of subjects	215
EEA total number of subjects	215

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)	2
Children (2-11 years)	14
Adolescents (12-17 years)	9
Adults (18-64 years)	169
From 65 to 84 years	21

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at two participating centers (Stockholm and Turku) between September 2007 and January 2014.

Pre-assignment

Screening details:

Six patients were excluded from the trial after randomization but before administration of their assigned GvHD prophylaxis. These 6 patients were considered as protocol violations, and they were excluded from further analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CsA/Mtx

Arm description:

graft-versus-host disease (GvHD) prophylaxis regimen using cyclosporine/methotrexate (CsA/Mtx)

Arm type	Active comparator
Investigational medicinal product name	CICLOSPORIN
Investigational medicinal product code	
Other name	Sandimmun Neoral, CsA
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients in the standard arm started CsA on day −1 (the day before graft infusion). CsA was given twice a day (mainly orally).
During the first two months, monitored plasma concentration levels were kept between 80-100 ng/mL in patients who received grafts from HLA-identical siblings, and between 150-250 ng/mL in MUD transplants. CsA was discontinued after tapering 3-4 months after HSCT in recipients of HLA-identical sibling grafts, and after six months in recipients of MUD transplants, in the absence of GvHD.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Mtx
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients in the standard arm: Mtx 15 mg/m2 was given on day +1, with consecutive doses of 10 mg/m2 given on days +3, +6, and +11 for all diagnoses.

Arm title	Tac/Sir

Arm description:

Graft-versus-host disease (GvHD) prophylaxis regimen using tacrolimus/sirolimus (Tac/Sir).

Arm type	Experimental

Investigational medicinal product name	SIROLIMUS
Investigational medicinal product code	
Other name	Rapamune, Rapamycin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the experimental arm started Tac/Sir in combination on day −3 before graft infusion. Sirolimus was given orally once daily, starting with a bolus dose of 6 mg in adults and 0.1 mg/kg in children, followed by continuous individual adjustment with monitored plasma target levels of 3-12 ng/mL.

Investigational medicinal product name	TACROLIMUS
Investigational medicinal product code	
Other name	Prograf, FK-506
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients in the experimental arm started Tac/Sir in combination on day −3 before graft infusion. Tacrolimus was given orally twice a day, starting at 0.15 mg/kg/day, with a target plasma concentration of 5-15 ng/mL.

Number of subjects in period 1[1]	CsA/Mtx	Tac/Sir
Started	106	103
Completed	106	103

Notes:

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

Justification: Six patients were excluded from the trial after randomization but before administration of their assigned GvHD prophylaxis. These 6 patients were considered as protocol violations, and they were excluded from further analysis.

Baseline characteristics

Reporting groups	
Reporting group title	CsA/Mtx
Reporting group description:	
graft-versus-host disease (GvHD) prophylaxis regimen using cyclosporine/methotrexate (CsA/Mtx)	
Reporting group title	Tac/Sir
Reporting group description:	
Graft-versus-host disease (GvHD) prophylaxis regimen using tacrolimus/sirolimus (Tac/Sir).	

Reporting group values	CsA/Mtx	Tac/Sir	Total
Number of subjects	106	103	209
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	52	50	
full range (min-max)	0.6 to 71	2.8 to 68	-
Gender categorical Units: Subjects			
Female	46	36	82
Male	60	67	127
Diagnosis			
Indication for transplant			
Units: Subjects			
CLL	7	15	22
Lymphoma	14	13	27
MDS	20	14	34
Other malignancies	6	8	14
Non-malignant	10	3	13
AML	30	27	57
ALL	19	23	42
Donor Units: Subjects			
Sibling	29	33	62
MUD (8/8)	58	39	97
URD (7/8, HLA-C mismatch)	15	29	44
URD (7/8, HLA-DR allele mismatch)	4	2	6

type of HSCT graft Units: Subjects			
BM	21	18	39
PBSCs	85	85	170

End points

End points reporting groups	
Reporting group title	CsA/Mtx
Reporting group description: graft-versus-host disease (GvHD) prophylaxis regimen using cyclosporine/methotrexate (CsA/Mtx)	
Reporting group title	Tac/Sir
Reporting group description: Graft-versus-host disease (GvHD) prophylaxis regimen using tacrolimus/sirolimus (Tac/Sir).	

Primary: Acute GVHD of grades II-IV

End point title	Acute GVHD of grades II-IV
End point description:	
End point type	Primary
End point timeframe: within 200 days post allogeneic HSCT	

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	41 (32 to 50)	51 (41 to 61)		

Statistical analyses

Statistical analysis title	Cumulative incidence of acute GVHD of grades II-IV
Statistical analysis description: Cumulative incidence of acute GVHD of grades II-IV in the two treatment arms within 200 days post allogeneic HSCT	
Comparison groups	CsA/Mtx v Tac/Sir
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.19
Method	Estimator of cumulative incidence curves

Notes:

[1] - Intention-to-treat analysis

Secondary: Time to neutrophil engraftment

End point title	Time to neutrophil engraftment

End point description:

End point type	Secondary

End point timeframe:

From start to end of the study

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: day				
median (full range (min-max))	18 (10 to 305)	17 (11 to 32)		

Statistical analyses

Statistical analysis title	Difference in time to neutrophil engraftment
Comparison groups	CsA/Mtx v Tac/Sir
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.24
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Intention-to-treat analysis

Secondary: Time to platelets engraftment

End point title	Time to platelets engraftment

End point description:

End point type	Secondary

End point timeframe:

From start to end of the study

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: day				
median (full range (min-max))	14 (0 to 190)	12 (0 to 68)		

Statistical analyses

Statistical analysis title	Difference in time to platelet engraftment
Comparison groups	Tac/Sir v CsA/Mtx
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Notes:
[3] - Intent-to-treat analysis

Secondary: Incidence of aGVHD (gr. III-IV)

End point title	Incidence of aGVHD (gr. III-IV)

End point description:

End point type	Secondary

End point timeframe:
From start to end of study

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	13 (7 to 19)	7 (2 to 12)		

Statistical analyses

Statistical analysis title	Difference in incidence of aGvHD (gr. III-IV)
Comparison groups	CsA/Mtx v Tac/Sir
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.09
Method	Estimator of cumulative incidence curves

Notes:
[4] - Intent-to-treat analysis

Secondary: Incidence of cGVHD (gr. III-IV)

End point title	Incidence of cGVHD (gr. III-IV)

End point description:

End point type	Secondary

End point timeframe:
From start to end of study

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	41 (31 to 51)	37 (26 to 48)		

Statistical analyses

Statistical analysis title	Difference in incidence of cGvHD (gr. III-IV)
Comparison groups	Tac/Sir v CsA/Mtx
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.51
Method	Estimator of cumulative incidence curves

Notes:
[5] - Intent-to-treat analysis

Secondary: Incidence of transplant-related mortality

End point title	Incidence of transplant-related mortality

End point description:

End point type	Secondary

End point timeframe:
Three years after HSCT

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	18 (11 to 25)	12 (6 to 18)		

Statistical analyses

Statistical analysis title	Difference in transplant-related mortality
Comparison groups	CsA/Mtx v Tac/Sir

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.4
Method	Estimator of cumulative incidence curves

Notes:

[6] - Intent-to-treat analysis

Secondary: Relapse-free survival

End point title	Relapse-free survival

End point description:

End point type	Secondary

End point timeframe:

Five years after HSCT

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	65 (55 to 75)	63 (53 to 73)		

Statistical analyses

Statistical analysis title	Difference in Relapse-free survival
Comparison groups	CsA/Mtx v Tac/Sir
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.73
Method	Kaplan-Meier method

Notes:

[7] - Intent-to-treat analysis

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Five years after transplantation

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percent				
number (confidence interval 95%)	72 (63 to 81)	71 (62 to 80)		

Statistical analyses

Statistical analysis title	Difference in Overall survival
Comparison groups	CsA/Mtx v Tac/Sir
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.71
Method	Kaplan-Meier method

Notes:
[8] - Intent-to-treat analysis

Secondary: Incidence of oral mucositis

End point title	Incidence of oral mucositis

End point description:

End point type	Secondary

End point timeframe:
Assessed three times a week until day +24 or until hospital discharge.

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Number of patients	61	66		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of infections

End point title	Incidence of infections

End point description:

End point type	Secondary

End point timeframe:
Once a week for three months after HSCT

End point values	CsA/Mtx	Tac/Sir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Number of post-transplant infections				
CMV	48	49		
BSI	19	27		
PTLD	9	6		
IFI	9	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

2007-2015

Adverse event reporting additional description:

Adverse events were reported to study sponsor (Nordic Safety Unit at Wyeth Nordic) by fax, transmittal forms (1747B, 7443)

Assessment type	Systematic

Dictionary used

Dictionary name	Free text
Dictionary version	n/a

Reporting groups

Reporting group title	All study subjects

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: There were no non-serious adverse events in this study.

Serious adverse events	All study subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 209 (1.91%)		
number of deaths (all causes)	63		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombotic microangiopathy			
subjects affected / exposed	2 / 209 (0.96%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Venoocclusive liver disease			
subjects affected / exposed	2 / 209 (0.96%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All study subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 209 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/27662016