Clinical trial results:
A Randomized Phase II Study to Determine the Most Promising Postgrafting Immunosuppression for Prevention of Acute GVHD after Unrelated Donor G-CSF mobilized Peripheral Blood Mononuclear Cell (G-PBMC) Transplantation using Nonmyeloablative Conditioning for Patients with Hematologic Malignancies. A Multi-Center Trial.

Summary

EudraCT number	2005-003305-90
Trial protocol	DK DE
Global end of trial date	08 May 2015

Results information

Result version number	v1 (current)
This version publication date	28 December 2019
First version publication date	28 December 2019
Summary attachment (see zip file)	1938 Final Paper (Haematologica p1938.pdf)

Trial information

Trial identification

Sponsor protocol code	1938.00

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00105001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fred Hutchinson Cancer Research Center
Sponsor organisation address	1100 Fairview Ave. N., Seattle, United States, 98109
Public contact	Brittany Carroll-Watts, Fred Hutchinson Cancer Research Center, 1 206-667-6815, bmcarrol@fredhutch.org
Scientific contact	Brenda Sandmaier, MD, Fred Hutchinson Cancer Research Center, 1 206-667-4961, bsandmai@fredhutch.org

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	01 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2011
Global end of trial reached?	Yes
Global end of trial date	08 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine which of 3 GVHD prophylaxis regimens results in a reduction of acute grades II-IV GVHD to <40%.

Protection of trial subjects:

Please see the Data and Safety Monitoring Plan of the protocol, pgs. 57 - 59.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	100 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	United States: 176
Worldwide total number of subjects	210
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	156
From 65 to 84 years	52

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients and donors are screened using the protocol's inclusion/exclusion criteria and, if accepted, randomized to an arm by data management.

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	Arm I (MMF and Tacrolimus)

Arm description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 180 with taper beginning on day 100 in the absence of GVHD. Patients also receive MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-96 with taper beginning on day 40 in the absence of GVHD.
Fludarabine Phosphate: Given IV
Total-Body Irradiation: Undergo total-body irradiation
Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Tacrolimus: Given IV or PO
Mycophenolate Mofetil: Given PO

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf, FK 506
Pharmaceutical forms	Concentrate for solution for infusion, Capsule, hard
Routes of administration	Oral use, Intravenous bolus use

Dosage and administration details:

Patients receive 0.06 mg/kg tacrolimus IV or PO every 12 hours on days -3 to 180 with taper beginning on day 100 in the absence of GVHD.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	Cellcept, MMF
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients receive 15 mg/kg MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-96 with taper beginning on day 40 in the absence of GVHD.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	2-F-ara-AMP, Beneflur, SH T 586
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive 30 mg/m^2 fludarabine administered over 30 minutes on Days -4, -3, and -2.

Arm title	Arm II (MMF and tacrolimus alternate schedule)

Arm description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD. Patients also receive Mycophenolate Mofetil [MMF] PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf, FK 506
Pharmaceutical forms	Capsule, hard, Concentrate for solution for infusion
Routes of administration	Intravascular use , Oral use

Dosage and administration details:

Patients receive 0.06 mg/kg tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	Cellcept, MMF
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients receive 15 mg/kg MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	2-F-ara-AMP, Beneflur, SH T 586
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive 30 mg/m^2 fludarabine administered over 30 minutes on Days -4, -3, and -2.

Arm title	Arm III (MMF, tacrolimus, and sirolimus)

Arm description:

Patients receive tacrolimus and Mycophenolate Mofetil [MMF] as in arm II. Patients also receive sirolimus PO once daily on days -3 to 80.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Sirolimus: Given PO

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf, FK 506
Pharmaceutical forms	Capsule, hard, Concentrate for solution for infusion
Routes of administration	Intravascular use , Oral use

Dosage and administration details:

Patients receive 0.06 mg/kg tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	Cellcept, MMF
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients receive 15 mg/kg MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	AY 22989, RAPA, SILA 9268A, WY-090217
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients receive 2 mg sirolimus PO once daily on days -3 to 80.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	2-F-ara-AMP, Beneflur, SH T 586
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive 30 mg/m^2 fludarabine administered over 30 minutes on Days -4, -3, and -2.

Number of subjects in period 1	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)
Started	70	71	69
Completed	69	71	68
Not completed	1	0	1
Did not proceed to transplant	1	-	1

Baseline characteristics

Reporting groups

Reporting group title	Arm I (MMF and Tacrolimus)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 180 with taper beginning on day 100 in the absence of GVHD. Patients also receive MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-96 with taper beginning on day 40 in the absence of GVHD.
Fludarabine Phosphate: Given IV
Total-Body Irradiation: Undergo total-body irradiation
Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Tacrolimus: Given IV or PO
Mycophenolate Mofetil: Given PO

Reporting group title	Arm II (MMF and tacrolimus alternate schedule)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD. Patients also receive Mycophenolate Mofetil [MMF] PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Reporting group title	Arm III (MMF, tacrolimus, and sirolimus)

Reporting group description:

Patients receive tacrolimus and Mycophenolate Mofetil [MMF] as in arm II. Patients also receive sirolimus PO once daily on days -3 to 80.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Sirolimus: Given PO

Reporting group values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects	70	71	69

Age categorical Units: Subjects			
<= 18 years	0	1	1
18 - 65 years	57	50	49
>=65 years	13	20	19
Age continuous Units: years			
median	60	60	60
full range (min-max)	26 to 74	13 to 72	15 to 75
Gender categorical Units: Subjects			
Female	29	30	23
Male	41	41	46

Reporting group values	Total		
Number of subjects	210		
Age categorical Units: Subjects			
<= 18 years	2		
18 - 65 years	156		
>=65 years	52		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	82		
Male	128		

End points

End points reporting groups

Reporting group title	Arm I (MMF and Tacrolimus)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 180 with taper beginning on day 100 in the absence of GVHD. Patients also receive MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-96 with taper beginning on day 40 in the absence of GVHD.
Fludarabine Phosphate: Given IV
Total-Body Irradiation: Undergo total-body irradiation
Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Tacrolimus: Given IV or PO
Mycophenolate Mofetil: Given PO

Reporting group title	Arm II (MMF and tacrolimus alternate schedule)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD. Patients also receive Mycophenolate Mofetil [MMF] PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Reporting group title	Arm III (MMF, tacrolimus, and sirolimus)

Reporting group description:

Patients receive tacrolimus and Mycophenolate Mofetil [MMF] as in arm II. Patients also receive sirolimus PO once daily on days -3 to 80.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Sirolimus: Given PO

Primary: Number of Participants With Grades II-IV Acute GVHD

End point title	Number of Participants With Grades II-IV Acute GVHD

End point description:

Percentage patients w/ grade II-IV aGHVD, estimated by cumulative incidence methods.

aGVHD Stages

Skin:
1. a maculopapular eruption involving < 25% BSA
2. a maculopapular eruption involving 25 - 50% BSA
3. generalized erythroderma
4. generalized erythroderma w/ bullous formation and often w/ desquamation

Liver:
1. bilirubin 2.0 - 3.0 mg/100 mL
2. bilirubin 3 - 5.9 mg/100 mL
3. bilirubin 6 - 14.9 mg/100 mL
4. bilirubin > 15 mg/100 mL

Gut:
Diarrhea is graded 1 - 4 in severity. Nausea and vomiting and/or anorexia caused by GVHD is assigned as 1 in severity. The severity of gut involvement is assigned to the most severe involvement noted. Patients w/ visible bloody diarrhea are at least stage 2 gut and grade 3 overall.

aGVHD Grades
Grade II: Stage 1 - 2 skin w/ no gut/liver involvement
Grade III: Stage 2 - 4 gut involvement and/or stage 2 - 4 liver involvement
Grade IV: Pattern and severity of GVHD similar to grade 3 w/ extreme constitutional symptoms or death

End point type	Primary

End point timeframe:

From the start of conditioning to 150 days post-transplant

End point values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69[1]	71	68[2]	
Units: Participants	44	34	32	

Notes:

[1] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

[2] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm I (MMF and Tacrolimus) v Arm III (MMF, tacrolimus, and sirolimus) v Arm II (MMF and tacrolimus alternate schedule)
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [3]
Method	Regression, Cox

Notes:

[3] - Overall test of homogeneity among arms, reflecting events over the entire period of follow-up

Statistical analysis title	Statistical Analysis 2
Comparison groups	Arm I (MMF and Tacrolimus) v Arm II (MMF and tacrolimus alternate schedule)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.1

Statistical analysis title	Statistical Analysis 3
Comparison groups	Arm I (MMF and Tacrolimus) v Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1

Secondary: Number of Non-Relapse Mortalities

End point title	Number of Non-Relapse Mortalities

End point description:

Percentage of NRM as estimated by cumulative incidence methods with competing risks. Cumulative incidence methods are the standard way to estimate incidence of an endpoint in the presence of competing risks and censoring (ref)" Here is the reference. Gooley TA, Leisenring W, Crowley J, Storer BE: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine 18:695-706, 1999. PMID 10204198

End point type	Secondary

End point timeframe:

From the start of conditioning to 200 days post-transplant

End point values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69[4]	71	68[5]	
Units: Participants	3	6	2	

Notes:

[4] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

[5] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm II (MMF and tacrolimus alternate schedule) v Arm I (MMF and Tacrolimus) v Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 [6]
Method	Regression, Cox

Notes:

[6] - Overall test of homogeneity among arms, reflecting events over the entire period of follow-up

Secondary: Number Participants Utilizing High-Dose Corticosteroid

End point title	Number Participants Utilizing High-Dose Corticosteroid

End point description:

Percentage of patients utilizing high-dose corticosteroid (as a surrogate marker for reduction of acute GVHD), estimated by cumulative incidence methods.
Cumulative incidence methods are the standard way to estimate incidence of an endpoint in the presence of competing risks and censoring (ref)" Here is the reference. Gooley TA, Leisenring W, Crowley J, Storer BE: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine 18:695-706, 1999. PMID 10204198

End point type	Secondary

End point timeframe:

From the start of conditioning to 150 days post-transplant

End point values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69[7]	71	68[8]	
Units: Participants	38	35	22	

Notes:

[7] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

[8] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm I (MMF and Tacrolimus) v Arm II (MMF and tacrolimus alternate schedule) v Arm III (MMF, tacrolimus, and sirolimus)

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [9]
Method	Regression, Cox

Notes:

[9] - Overall test of homogeneity among arms, reflecting events over the entire period of follow-up

Statistical analysis title	Statistical Analysis 2
Comparison groups	Arm I (MMF and Tacrolimus) v Arm II (MMF and tacrolimus alternate schedule)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Statistical analysis title	Statistical Analysis 3
Comparison groups	Arm I (MMF and Tacrolimus) v Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.8

Secondary: Number of of Participants Surviving Overall

End point title	Number of of Participants Surviving Overall

End point description:

Percentage of patients surviving, estimated by cumulative incidence methods
Cumulative incidence methods are the standard way to estimate incidence of an endpoint in the presence of competing risks and censoring (ref)" Here is the reference. Gooley TA, Leisenring W, Crowley J, Storer BE: Estimation of failure probabilities in the presence of competing risks: new

representations of old estimators. Statistics in Medicine 18:695-706, 1999. PMID 10204198

End point type	Secondary

End point timeframe:

From the start of conditioning to 2 Years post-transplant.

End point values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69[10]	71	68[11]	
Units: Participants	36	32	30	

Notes:

[10] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.
[11] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm I (MMF and Tacrolimus) v Arm II (MMF and tacrolimus alternate schedule) v Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93 [12]
Method	Regression, Cox

Notes:

[12] - Overall test of homogeneity among arms, reflecting events over the entire period of follow-up

Secondary: Number of Participants Surviving Without Progression

End point title	Number of Participants Surviving Without Progression

End point description:

Percentage of patients with progression-free survival, estimated by cumulative incidence methods Cumulative incidence methods are the standard way to estimate incidence of an endpoint in the presence of competing risks and censoring (ref)" Here is the reference. Gooley TA, Leisenring W, Crowley J, Storer BE: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine 18:695-706, 1999. PMID 10204198

End point type	Secondary

End point timeframe:

From the start of conditioning to 2 Years post-transplant

End point values	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69[13]	71	68[14]	
Units: Participants	28	27	26	

Notes:

[13] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

[14] - One subject counted towards accrual but did not proceed to transplant and thus was not evaluable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm I (MMF and Tacrolimus) v Arm II (MMF and tacrolimus alternate schedule) v Arm III (MMF, tacrolimus, and sirolimus)
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96 [15]
Method	Regression, Cox

Notes:

[15] - Overall test of homogeneity among arms, reflecting events over the entire period of follow-up

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: From the start of conditioning to 100 Days post-transplant
SAEs: From the start of conditioning to 200 Days post-transplant
All-Cause Mortality: Conditioning through 1 Year

Assessment type	Systematic

Dictionary used

Dictionary name	Adapted CTC
Dictionary version	2.0

Reporting groups

Reporting group title	Arm I (MMF and Tacrolimus)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 180 with taper beginning on day 100 in the absence of GVHD. Patients also receive MMF PO every 8 hours on days 0-29 and then every 12 hours on days 30-96 with taper beginning on day 40 in the absence of GVHD.
Fludarabine Phosphate: Given IV
Total-Body Irradiation: Undergo total-body irradiation
Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation
Tacrolimus: Given IV or PO
Mycophenolate Mofetil: Given PO

Reporting group title	Arm II (MMF and tacrolimus alternate schedule)

Reporting group description:

Patients receive tacrolimus IV or PO every 12 hours on days -3 to 150 with taper beginning on day 100 in the absence of GVHD. Patients also receive Mycophenolate Mofetil [MMF] PO every 8 hours on days 0-29 and then every 12 hours on days 30-180 with taper beginning on day 150 in the absence of GVHD.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Reporting group title	Arm III (MMF, tacrolimus, and sirolimus)

Reporting group description:

Patients receive tacrolimus and Mycophenolate Mofetil [MMF] as in arm II. Patients also receive sirolimus PO once daily on days -3 to 80.

Fludarabine Phosphate: Given IV

Total-Body Irradiation: Undergo total-body irradiation

Peripheral Blood Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Allogeneic Hematopoietic Stem Cell Transplantation: Undergo allogeneic peripheral blood stem cell transplantation

Tacrolimus: Given IV or PO

Mycophenolate Mofetil: Given PO

Serious adverse events	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 69 (13.04%)	8 / 71 (11.27%)	7 / 68 (10.29%)
number of deaths (all causes)	21	24	28
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Severe hemoptysis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
CNS cerebrovascular ischemia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	2 / 69 (2.90%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			

subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Toxic leukoencephalopathy, infections w/ pneumonia and pyelonephritis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (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
Immune system disorders			
GVHD			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GVHD w/ Infection			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	1 / 1
Gastrointestinal disorders			
Intestinal pneumatosis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (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
Renal and urinary disorders			
Renal insufficiency			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Mucormycosis			

subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory infection			
subjects affected / exposed	1 / 69 (1.45%)	3 / 71 (4.23%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	3 / 3	0 / 0
Sepsis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

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

Non-serious adverse events	Arm I (MMF and Tacrolimus)	Arm II (MMF and tacrolimus alternate schedule)	Arm III (MMF, tacrolimus, and sirolimus)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 69 (36.23%)	22 / 71 (30.99%)	25 / 68 (36.76%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Treatment related secondary malignancy			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hematoma			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences (all)	2	3	1
Thromboembolic event			

subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences (all)	0	1	1
Fever			
subjects affected / exposed	0 / 69 (0.00%)	3 / 71 (4.23%)	0 / 68 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	5 / 69 (7.25%)	8 / 71 (11.27%)	4 / 68 (5.88%)
occurrences (all)	5	9	4
Pleural effusion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	2 / 68 (2.94%)
occurrences (all)	0	1	2
Pneumonitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders - Other, specify (Pulmonary, NOS)			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Psychosis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 69 (2.90%)	2 / 71 (2.82%)	1 / 68 (1.47%)
occurrences (all)	2	2	1
Creatinine increased			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	4 / 68 (5.88%)
occurrences (all)	1	1	4
Neutrophil count decreased			
subjects affected / exposed	1 / 69 (1.45%)	3 / 71 (4.23%)	0 / 68 (0.00%)
occurrences (all)	1	3	0
Platelet count decreased			
subjects affected / exposed	0 / 69 (0.00%)	2 / 71 (2.82%)	0 / 68 (0.00%)
occurrences (all)	0	2	0
White blood cell decreased			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences (all)	0	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Cardiac arrest			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Heart failure			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Pericardial tamponade			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Ventricular arrhythmia			

subjects affected / exposed	2 / 69 (2.90%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	2 / 68 (2.94%)
occurrences (all)	0	1	2
Seizure			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	1	0	3
Syncope			
subjects affected / exposed	2 / 69 (2.90%)	0 / 71 (0.00%)	2 / 68 (2.94%)
occurrences (all)	2	0	3
Tremor			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	1	1	0
Hemolysis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	1	1	0
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	1	1	0
Diarrhea			

subjects affected / exposed	5 / 69 (7.25%)	1 / 71 (1.41%)	4 / 68 (5.88%)
occurrences (all)	5	1	4
Enterocolitis			
subjects affected / exposed	2 / 69 (2.90%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Mucositis oral			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	3 / 68 (4.41%)
occurrences (all)	1	1	3
Vomiting			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 69 (1.45%)	1 / 71 (1.41%)	1 / 68 (1.47%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Generalized muscle weakness			
subjects affected / exposed	1 / 69 (1.45%)	2 / 71 (2.82%)	0 / 68 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal and connective tissue disorder - Other, specify (Cervical disk herniation)			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1

Musculoskeletal and connective tissue disorder - Other, specify (Pain, NOS)			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Duodenal infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	1	0	1
Hyperglycemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Hypertriglyceridemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 71 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Hypokalemia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Hyponatremia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 71 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0

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