



## Clinical trial results:

### A Randomized Phase III Study to Determine the Most Promising Postgrafting Immunosuppression for Prevention of Acute GVHD after Unrelated Donor Hematopoietic Cell Transplantation using Nonmyeloablative Conditioning for Patients with Hematologic Malignancies A Multi-Center Trial

#### Summary

EudraCT number	2011-000088-28
Trial protocol	DK DE
Global end of trial date	30 June 2017

#### Results information

Result version number	v1 (current)
This version publication date	22 January 2022
First version publication date	22 January 2022
Summary attachment (see zip file)	Addition of sirolimus to standard cyclosporine plus mycophenolate mofetil-based graft-versus-host disease prophylaxis for patients after unrelated non-myeloablative haemopoietic stem cell transplant (Sandmaier_Lancet-Haematology-2019.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	FHCRC2448
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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,
Public contact	Kim Drever, Fred Hutchinson Cancer Research Center, +1 (206) 667-6825, kdrever@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 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2016
Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To determine which of two Graft versus host disease prophylaxis regimens results in a reduction of acute grades II-IV GVHD

Protection of trial subjects:

Patient were followed closely in very specialized department of bone marrow transplant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2011
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: 22
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 149
Worldwide total number of subjects	174
EEA total number of subjects	25

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)	0

Adults (18-64 years)	106
From 65 to 84 years	68
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
<b>Arm title</b>	Arm 0

Arm description:

Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Arm removed as of 14-Sep-2011

Arm type	Experimental
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<sup>2</sup> fludarabine administered over 30 minutes on Days -4, -3, and -2.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	CSP
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

CSP is given based on adjusted body weight, at 5.0 mg/kg PO q12 hours from day -3. If there is nausea and vomiting at anytime during CSP treatment the drug should be given intravenously at the appropriate dose that was used to obtain a therapeutic level. In the absence of acute or chronic GVHD, CSP is tapered at day 96 over 55 days (to be completed on Day +150).

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamycin, Rapamune
Pharmaceutical forms	Capsule, hard, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients received sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Sirolimus should be given at least 4 hours after an oral dose of cyclosporine as concurrent administration leads to elevation of sirolimus levels.

<b>Arm title</b>	Arm 1
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Arm description:

Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and MMF PO three times daily (TID) on days 0-29 and then BID on days 30-150 with taper to day 180.

Arm type	Experimental
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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<sup>2</sup> fludarabine administered over 30 minutes on Days -4, -3, and -2.

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:**

MMF will be given based on adjusted body weight, at 15 mg/kg PO at 4-6 hours after SCT infusion is complete, then to be given at 15 mg/kg PO Q8 hours and then reduce to Q12 hours on day +30. Continue MMF Q12 hours until day +150 then taper until day +180 GVHD or disease relapse/progression occurs.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	CSP
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

CSP is given based on adjusted body weight, at 5.0 mg/kg PO q12 hours from day -3. If there is nausea and vomiting at anytime during CSP treatment the drug should be given intravenously at the appropriate dose that was used to obtain a therapeutic level. In the absence of acute or chronic GVHD, CSP is tapered at day 96 over 55 days (to be completed on Day +150).

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamycin, Rapamune
Pharmaceutical forms	Capsule, hard, Oral solution
Routes of administration	Oral use

**Dosage and administration details:**

Patients received sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Sirolimus should be given at least 4 hours after an oral dose of cyclosporine as concurrent administration leads to elevation of sirolimus levels.

<b>Arm title</b>	Arm 2
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**Arm description:**

Patients receive CSP as in Arm I and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Patients also receive MMF PO TID on days 0-29 and then BID on days 30-40. MMF will then be discontinued without taper unless GVHD or disease relapse/progression occurs.

Arm type	Experimental
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<sup>2</sup> fludarabine administered over 30 minutes on Days -4, -3, and -2.

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

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**Dosage and administration details:**

MMF will be given based on adjusted body weight, at 15 mg/kg PO at 4-6 hours after SCT infusion is complete, then to be given at 15 mg/kg PO Q8 hours and then reduce to Q12 hours on day +30. Continue MMF Q12 hours until day +40, MMF will then be discontinued without taper unless GVHD or disease relapse/progression occurs.

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	CSP
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

CSP is given based on adjusted body weight, at 5.0 mg/kg PO q12 hours from day -3. If there is nausea and vomiting at anytime during CSP treatment the drug should be given intravenously at the appropriate dose that was used to obtain a therapeutic level. In the absence of acute or chronic GVHD, CSP is tapered at day 96 over 55 days (to be completed on Day +150).

<b>Number of subjects in period 1</b>	Arm 0	Arm 1	Arm 2
Started	6	77	91
Completed	6	77	90
Not completed	0	0	1
Aborted transplant during conditioning and subsequ	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Arm 0
Reporting group description:	
Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Arm removed as of 14-Sep-2011	
Reporting group title	Arm 1
Reporting group description:	
Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and MMF PO three times daily (TID) on days 0-29 and then BID on days 30-150 with taper to day 180.	
Reporting group title	Arm 2
Reporting group description:	
Patients receive CSP as in Arm I and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Patients also receive MMF PO TID on days 0-29 and then BID on days 30-40. MMF will then be discontinued without taper unless GVHD or disease relapse/progression occurs.	

Reporting group values	Arm 0	Arm 1	Arm 2
Number of subjects	6	77	91
Age categorical			
Units: Subjects			
Less than 18	0	0	0
Between 18 and 65	4	52	50
Greater than 65	2	25	41
Age continuous			
Units: years			
median	59.515	61.94	63.75
full range (min-max)	36.47 to 67.83	18.2 to 77.09	41.02 to 79
Gender categorical			
Units: Subjects			
Female	2	27	28
Male	4	50	63

Reporting group values	Total		
Number of subjects	174		
Age categorical			
Units: Subjects			
Less than 18	0		
Between 18 and 65	106		
Greater than 65	68		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	57		
Male	117		

## End points

### End points reporting groups

Reporting group title	Arm 0
Reporting group description:	
Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Arm removed as of 14-Sep-2011	
Reporting group title	Arm 1
Reporting group description:	
Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and MMF PO three times daily (TID) on days 0-29 and then BID on days 30-150 with taper to day 180.	
Reporting group title	Arm 2
Reporting group description:	
Patients receive CSP as in Arm I and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Patients also receive MMF PO TID on days 0-29 and then BID on days 30-40. MMF will then be discontinued without taper unless GVHD or disease relapse/progression occurs.	

### Primary: Number of Patients With Grades II-IV Acute GVHD

End point title	Number of Patients With Grades II-IV Acute GVHD
End point description:	
Number of patients with grades II-IV acute GVHD	
aGVHD Stages	
Skin:	
a maculopapular eruption involving < 25% BSA	
a maculopapular eruption involving 25 - 50% BSA	
generalized erythroderma	
generalized erythroderma w/ bullous formation and often w/ desquamation	
Liver:	
bilirubin 2.0 - 3.0 mg/100 mL	
bilirubin 3 - 5.9 mg/100 mL	
bilirubin 6 - 14.9 mg/100 mL	
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:	
100 days post-transplant	

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[1]</sup>	
Units: Subjects	3	39	22	

Notes:

[1] - One subject counted towards accrual but not evaluated with respect to outcome measures.

## Statistical analyses

<b>Statistical analysis title</b>	Cumulative incidence of grade 2–4 acute GVHD
Statistical analysis description: Cumulative incidence of grade 2–4 acute graft versus host disease at day 100	
Comparison groups	Arm 2 v Arm 1
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Regression, Cox

## Secondary: Number of Patients With Chronic Extensive GVHD

End point title	Number of Patients With Chronic Extensive GVHD
End point description: Number of patients who developed chronic extensive GVHD post-transplant. The diagnosis of chronic GVHD requires at least one manifestation that is distinctive for chronic GVHD as opposed to acute GVHD. In all cases, infection and others causes must be ruled out in the differential diagnosis of chronic GVHD.	
End point type	Secondary
End point timeframe: One year post-transplant	

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[2]</sup>	
Units: Subjects	3	38	43	

Notes:

[2] - One subject counted towards accrual but not evaluated with respect to outcome measures.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Patients With Grades III-IV Acute GVHD

End point title	Number of Patients With Grades III-IV Acute GVHD
End point description: Number of patients with grades III-IV acute GVHD aGVHD Stages Skin: a maculopapular eruption involving < 25% BSA a maculopapular eruption involving 25 - 50% BSA generalized erythroderma generalized erythroderma w/ bullous formation and often w/ desquamation Liver: bilirubin 2.0 - 3.0 mg/100 mL bilirubin 3 - 5.9 mg/100 mL bilirubin 6 - 14.9 mg/100 mL 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	Secondary
End point timeframe:	
100 days post-transplant	

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[3]</sup>	
Units: Subjects	0	8	2	

Notes:

[3] - One subject counted towards accrual but not evaluated with respect to outcome measures.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Non-Relapse Mortalities

End point title	Number of Non-Relapse Mortalities
End point description:	
Number of subjects expired without disease progression/relapse.	
End point type	Secondary
End point timeframe:	
One year post-transplant	

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[4]</sup>	
Units: Subjects	0	12	4	

Notes:

[4] - One subject counted towards accrual but not evaluated with respect to outcome measures.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of of Participants Surviving Overall

End point title	Number of of Participants Surviving Overall
End point description:	
One year post-transplant	
End point type	Secondary

End point timeframe:

Number of subjects surviving overall post-transplant.

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[5]</sup>	
Units: Subjects	6	53	75	

Notes:

[5] - One subject counted towards accrual but not evaluated with respect to outcome measures.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Relapse/Progression

End point title	Number of Participants With Relapse/Progression
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End point description:

Relapse/Progression criteria:

CML New cytogenetic abnormality and/or development of accelerated phase or blast crisis. The criteria for accelerated phase will be defined as unexplained fever >38.3°C, new clonal cytogenetic abnormalities in addition to a single Ph-positive chromosome, marrow blasts and promyelocytes >20%. AML, ALL, MDS >5% blasts by morphologic or flow cytometric evaluation of the BMA or appearance of extramedullary disease CLL ≥1 of: Physical exam/imaging studies ≥50% increase or new, circulating lymphocytes by morphology and/or flow cytometry ≥50% increase, and lymph node biopsy w/ Richter's transformation.

NHL >25% increase in the sum of the products of the perpendicular diameters of marker lesions, or the appearance of new lesions.

MM

≥100% increase of the serum myeloma protein from its lowest level, or reappearance of myeloma peaks that had disappeared w/ treatment; or definite increase in the size or numb

End point type	Secondary
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End point timeframe:

One year post-transplant

End point values	Arm 0	Arm 1	Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	77	90 <sup>[6]</sup>	
Units: Subjects	1	16	16	

Notes:

[6] - One subject counted towards accrual but not evaluated with respect to outcome measures.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs: Conditioning through Day 100

SAEs: Conditioning through Day 200

All-Cause Mortality: Conditioning through 1 Year.

Assessment type	Systematic
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### Dictionary used

Dictionary name	Adapted CTC
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Dictionary version	4.0
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### Reporting groups

Reporting group title	Arm 0
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Reporting group description:

Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Arm removed as of 14-Sep-2011

Reporting group title	Arm 1
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Reporting group description:

Patients receive CSP orally (PO) twice daily (BID) on days -3 to 96 with taper to day 150 and MMF PO three times daily (TID) on days 0-29 and then BID on days 30-150 with taper to day 180.

Reporting group title	Arm 2
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Reporting group description:

Patients receive CSP as in Arm I and sirolimus PO once daily (QD) on days -3 to 150 with taper to day 180. Patients also receive MMF PO TID on days 0-29 and then BID on days 30-40. MMF will then be discontinued without taper unless GVHD or disease relapse/progression occurs.

Serious adverse events	Arm 0	Arm 1	Arm 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	0 / 90 (0.00%)
number of deaths (all causes)	0	23	13
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Arm 0	Arm 1	Arm 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	27 / 77 (35.06%)	26 / 90 (28.89%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Treatment related secondary malignancy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 77 (2.60%)	0 / 90 (0.00%)
occurrences (all)	0	3	0
Thromboembolic event			
subjects affected / exposed	0 / 6 (0.00%)	2 / 77 (2.60%)	1 / 90 (1.11%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 6 (16.67%)	3 / 77 (3.90%)	0 / 90 (0.00%)
occurrences (all)	1	3	0
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	2 / 90 (2.22%)
occurrences (all)	0	1	2
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 77 (7.79%)	3 / 90 (3.33%)
occurrences (all)	0	6	0
Laryngeal inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 77 (0.00%)	0 / 90 (0.00%)
occurrences (all)	1	0	0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	3 / 77 (3.90%)	0 / 90 (0.00%)
occurrences (all)	0	3	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Pulmonary edema			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Respiratory failure subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 77 (2.60%) 2	1 / 90 (1.11%) 1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 77 (2.60%) 2	0 / 90 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	1 / 90 (1.11%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	7 / 77 (9.09%) 7	1 / 90 (1.11%) 1
Creatinine increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	4 / 77 (5.19%) 4	4 / 90 (4.44%) 4
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	1 / 90 (1.11%) 1
Ventricular arrhythmia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 77 (1.30%) 1	1 / 90 (1.11%) 1
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	6 / 77 (7.79%) 7	3 / 90 (3.33%) 3
Hemolysis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 77 (3.90%) 3	0 / 90 (0.00%) 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Colonic hemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Diarrhea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 77 (2.60%)	1 / 90 (1.11%)
occurrences (all)	0	2	1
Fecal incontinence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Gastric ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Mucositis oral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	2 / 90 (2.22%)
occurrences (all)	0	1	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	3 / 90 (3.33%)
occurrences (all)	0	0	3
Chronic kidney disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 77 (0.00%)	1 / 90 (1.11%)
occurrences (all)	0	0	1
Hemorrhagic cystitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 77 (1.30%)	0 / 90 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Encephalitis infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Enterocolitis infectious subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 77 (0.00%) 0	1 / 90 (1.11%) 1
Pleural infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 77 (0.00%) 0	1 / 90 (1.11%) 1
Sepsis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Skin infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Weight loss subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 77 (1.30%) 1	0 / 90 (0.00%) 0
Metabolism and nutrition disorders Hypertriglyceridemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 77 (0.00%) 0	4 / 90 (4.44%) 4

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2011	The study was modified from 3-arm randomized phase II to 2-arm randomized phase III.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported