Clinical trial results:
Triple arm, prospective-randomised multi centre study phase IV to evaluate calcineurin inhibitor reduced, steroid free immunosuppression after renal transplantation in low-risk patients (HARMONY-Study)

Summary

EudraCT number	2007-006516-31
Trial protocol	DE
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	IT1850071

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00724022
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Center – University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Prof. Dr. Oliver Thomusch, Medical Center – University of Freiburg, +49 76127028060, oliver.thomusch@uniklinik-freiburg.de
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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	31 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Ratio and severe of acute bioptical confirmed rejection reactions (to BANFF) as well as time to first bioptical assured rejection

Protection of trial subjects:

The trial was performed in accordance with the Declaration of Helsinki as well as with the German Drug law and guidelines for the clinical testing of drugs. This trial was designed and monitored in accordance with the principles which have their origin in the Declaration of Helsinki and in accordance with sponsor and CRO standard operating procedures (SOPs). These SOPs comply with the ethical principles of Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2008
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	Germany: 587
Worldwide total number of subjects	587
EEA total number of subjects	587

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)	452
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

21 German centers enrolled and randomized 615 patients between January 1, 2008, and November 30, 2013.

Pre-assignment

Screening details:

The patients had to meet all inclusion criteria; patients meeting any exclusion criterion had to be excluded from the study. The inclusion and exclusion criteria referred to drug safety aspects, guidelines by regulatory authorities and the International Conference on Harmonization (ICH) / Good Clinical Practice (GCP).

Pre-assignment period milestones

Number of subjects started	615[1]
Number of subjects completed	587

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No med. treatment, no kidney transplant.: 28

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 21 German centers enrolled and randomised 615 patients between 1 January 2008 and 30 November 2013; 587 patients were included in the IIT analyses.

Period 1

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

Blinding implementation details:

After signing informed consent and after screening assessments patients were randomized 1:1:1 into either treatment arm A, B or C (no blinding).

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Basiliximab and steroids

Arm description:

Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and corticosteroid maintenance therapy

Arm type	Active comparator
Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	Simulect
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Strength: 10mg, 20mg

1st dose (during initiation of the kidney transplantation): 20mg
2nd dose (day 4 after renal transplantation): 20mg

Investigational medicinal product name	MMF
Investigational medicinal product code	
Other name	CellCept

Pharmaceutical forms	Film-coated tablet
Routes of administration	Ocular use

Dosage and administration details:

Strength: 500mg

Preoperative and postoperative: 2 x 1000mg
Day 1 until end of month 12: 2 x 1000mg

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf
Pharmaceutical forms	Prolonged-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Strength: 0.5mg, 1mg, 3mg, 5mg

Operation day: 1 x 0.2 mg/kg body weight/day (preoperative)
Day 1: 1 x 0.2 mg/kg body weight/day
Day 2: 1 x 0.2 mg/kg body weight/day
Day 3: 1 x 0.2 mg/kg body weight/day

The further dose depends on the plasma concentration of TAC as follows had to be reached:
Until end of month 1: 7-12 ng/ml
Month 2+3: 6-10 ng/ml
Month 4-12: 3-8 ng/ml

Investigational medicinal product name	Decortin H
Investigational medicinal product code	
Other name	Solu-Decortin H
Pharmaceutical forms	Powder and solvent for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Strength:
Solu-Decortin®: 10mg, 25mg, 50mg, 100mg, 250mg, 500mg, 1000mg
Decortin ® H: 1mg, 5mg, 20mg, 50mg

Day 0: 250 mg i.v. pre- and 250mg i.v. intraoperative
Day 1: 100 mg i.v.
Day 2: 75 mg p.o.
Day 3: 50 mg p.o.
Day 4-7: 25 mg p.o.
From day 8: no further treatment

Arm title	Arm B: Basiliximab and rapid steroid withdrawal

Arm description:

Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and rapid corticosteroid withdrawal on day 8

Arm type	Active comparator
Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	Simulect
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Strength: 10mg, 20mg

1st dose (during initiation of the kidney transplantation): 20mg
2nd dose (day 4 after renal transplantation): 20mg

Investigational medicinal product name	MMF
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Film-coated tablet
Routes of administration	Ocular use

Dosage and administration details:

Strength: 500mg

Preoperative and postoperative: 2 x 1000mg
Day 1 until end of month 12: 2 x 1000mg

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf
Pharmaceutical forms	Prolonged-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Strength: 0.5mg, 1mg, 3mg, 5mg

Operation day: 1 x 0.2 mg/kg body weight/day (preoperative)
Day 1: 1 x 0.2 mg/kg body weight/day
Day 2: 1 x 0.2 mg/kg body weight/day
Day 3: 1 x 0.2 mg/kg body weight/day

The further dose depends on the plasma concentration of TAC as follows had to be reached:
Until end of month 1: 7-12 ng/ml
Month 2+3: 6-10 ng/ml
Month 4-12: 3-8 ng/ml

Investigational medicinal product name	Decortin H
Investigational medicinal product code	
Other name	Solu-Decortin H
Pharmaceutical forms	Tablet, Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Strength:
Solu-Decortin®: 10mg, 25mg, 50mg, 100mg, 250mg, 500mg, 1000mg
Decortin ® H: 1mg, 5mg, 20mg, 50mg

Day 0: 250 mg i.v. pre- and 250mg i.v. intraoperative
Day 1: 100 mg i.v.
Day 2: 75 mg p.o.
Day 3: 50 mg p.o.
Day 4-7: 25 mg p.o.
From day 8: no further treatment

Arm title	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal

Arm description:

Rabbit antithymocyte globulin (rabbit ATG) induction therapy, and rapid corticosteroid withdrawal on day 8

Arm type	Experimental
Investigational medicinal product name	rATG
Investigational medicinal product code	
Other name	Thymoglobulin
Pharmaceutical forms	Powder for solution for infusion, Solvent for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Strength: 5 mg/ml

Day 0 intraoperative: 1.5 mg/kg body weight
Day 1: 1.5 mg/kg body weight
Day 2: 1.5 mg/kg body weight
Day 3: 1.5 mg/kg body weight (provided lymphocytes > 200/µl)

Investigational medicinal product name	MMF
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Film-coated tablet
Routes of administration	Ocular use

Dosage and administration details:

Strength: 500mg

Preoperative and postoperative: 2 x 1000mg
Day 1 until end of month 12: 2 x 1000mg

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Advagraf
Pharmaceutical forms	Prolonged-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Strength: 0.5mg, 1mg, 3mg, 5mg

Operation day: 1 x 0.2 mg/kg body weight/day (preoperative)
Day 1: 1 x 0.2 mg/kg body weight/day
Day 2: 1 x 0.2 mg/kg body weight/day
Day 3: 1 x 0.2 mg/kg body weight/day

Investigational medicinal product name	Decortin H
Investigational medicinal product code	
Other name	Solu-Decortin H
Pharmaceutical forms	Powder for suspension for injection, Solvent for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Strength:
Solu-Decortin®: 10mg, 25mg, 50mg, 100mg, 250mg, 500mg, 1000mg
Decortin ® H: 1mg, 5mg, 20mg, 50mg

Day 0: 250 mg i.v. pre- and 250mg i.v. intraoperative
Day 1: 100 mg i.v.
Day 2: 75 mg p.o.
Day 3: 50 mg p.o.
Day 4-7: 25 mg p.o.
From day 8: no further treatment

Investigational medicinal product name	Basiliximab
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:

1st dose (during initiation of the kidney transplantation): 20mg
2nd dose (day 4 after renal transplantation): 20mg

Number of subjects in period 1	Arm A: Basiliximab and steroids	Arm B: Basiliximab and rapid steroid withdrawal	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal
Started	206	189	192
Completed	135	123	115
Not completed	71	66	77
Graft losses	6	5	9
Withdrawal by participants	18	15	15
Adverse events	11	5	11
Screening failures	3	1	3
Other	6	19	13
Deaths	11	4	5
Lost to follow-up	5	3	7
Lack of efficacy	2	4	3
Protocol deviation	9	10	11

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Basiliximab and steroids
Reporting group description:	
Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and corticosteroid maintenance therapy	
Reporting group title	Arm B: Basiliximab and rapid steroid withdrawal
Reporting group description:	
Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and rapid corticosteroid withdrawal on day 8	
Reporting group title	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal
Reporting group description:	
Rabbit antithymocyte globulin (rabbit ATG) induction therapy, and rapid corticosteroid withdrawal on day 8	

Reporting group values	Arm A: Basiliximab and steroids	Arm B: Basiliximab and rapid steroid withdrawal	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal
Number of subjects	206	189	192
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	159	139	154
From 65-84 years	47	50	38
85 years and over	0	0	0
Age continuous			
Demographic and other Baseline Characteristics of the intention to treat / safety population (N=587)			
Units: years			
arithmetic mean	54.5	54.0	53.6
standard deviation	± 11.9	± 12.8	± 11.9
Gender categorical Units: Subjects			
Female	65	67	68
Male	141	122	124

Reporting group values	Total		
Number of subjects	587		
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)	452		
From 65-84 years	135		
85 years and over	0		
Age continuous			
Demographic and other Baseline Characteristics of the intention to treat / safety population (N=587)			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	200		
Male	387		

Subject analysis sets

Subject analysis set title	Intention-to-treat / Safety
Subject analysis set type	Intention-to-treat

Subject analysis set description:

intention to treat / safety population: N=587

Reporting group values	Intention-to-treat / Safety		
Number of subjects	587		
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)	452		
From 65-84 years	135		
85 years and over	0		
Age continuous			
Demographic and other Baseline Characteristics of the intention to treat / safety population (N=587)			
Units: years			
arithmetic mean	54.1		
standard deviation	± 12.2		
Gender categorical			
Units: Subjects			
Female	200		
Male	387		

End points

End points reporting groups

Reporting group title	Arm A: Basiliximab and steroids
Reporting group description:	
Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and corticosteroid maintenance therapy	
Reporting group title	Arm B: Basiliximab and rapid steroid withdrawal
Reporting group description:	
Basiliximab induction with low-dose tacrolimus, mycophenolate mofetil, and rapid corticosteroid withdrawal on day 8	
Reporting group title	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal
Reporting group description:	
Rabbit antithymocyte globulin (rabbit ATG) induction therapy, and rapid corticosteroid withdrawal on day 8	
Subject analysis set title	Intention-to-treat / Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
intention to treat / safety population: N=587	

Primary: Biopsy proven rejection rate (excluding borderline)

End point title	Biopsy proven rejection rate (excluding borderline)
End point description:	
Biopsy proven rejection rates (excluding borderline) (additional analysis)	
End point type	Primary
End point timeframe:	
12 months	

End point values	Arm A: Basiliximab and steroids	Arm B: Basiliximab and rapid steroid withdrawal	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal	Intention-to-treat / Safety
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	206[1]	189[2]	192[3]	587[4]
Units: Rejections				
Yes	23	20	19	62
No	183	169	173	525

Notes:

[1] - IIT / Safety population

[2] - IIT / Safety population

[3] - IIT / Safety population

[4] - ITT / Safety population

Statistical analyses

Statistical analysis title	Primary efficacy analysis BPAR rate: group A vs C

Statistical analysis description:

The primary efficacy analysis was performed according to the intention-to-treat principle.

Comparison groups	Arm A: Basiliximab and steroids v Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal v Intention-to-treat / Safety
Number of subjects included in analysis	985
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7452
Method	Fisher exact

Statistical analysis title	Primary efficacy analysis BPAR rate: group B vs C
Statistical analysis description:	
The primary efficacy analysis was performed according to the intention-to-treat principle.	
Comparison groups	Arm B: Basiliximab and rapid steroid withdrawal v Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal v Intention-to-treat / Safety
Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8669
Method	Fisher exact

Primary: Severity of biopsy proven rejections (BANFF)

End point title	Severity of biopsy proven rejections (BANFF)
End point description:	

End point type	Primary
End point timeframe:	
Within the first year after renal transplantation	

End point values	Arm A: Basiliximab and steroids	Arm B: Basiliximab and rapid steroid withdrawal	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal	Intention-to-treat / Safety
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	206	189	192	587
Units: Number of patients				
Acute T-cell mediated rejection (Banff 1A)	8	9	5	22
Acute T-cell mediated rejection (Banff 1b)	1	1	1	3
Acute T-cell mediated rejection (Banff 2a)	7	7	2	16
Acute T-cell mediated rejection (Banff 2B)	0	1	0	1
Acute antibody-mediated rejection (BANFF 1)	2	1	1	4

Acute antibody-mediated rejection (BANFF 2)	1	1	2	4
Acute antibody-mediated rejection (BANFF 3)	0	0	1	1

Statistical analyses

Statistical analysis title	Severity of biopsy proven rejections
Comparison groups	Arm B: Basiliximab and rapid steroid withdrawal v Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal v Arm A: Basiliximab and steroids v Intention-to-treat / Safety
Number of subjects included in analysis	1174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Fisher exact

Post-hoc: Biopsy proven rejection rate (including borderline)

End point title	Biopsy proven rejection rate (including borderline)

End point description:

The primary objective was the rate and degree of severity of acute rejections confirmed by biopsy and also assessment of the time to first rejection confirmed by biopsy.

End point type	Post-hoc

End point timeframe:

12 months

End point values	Arm A: Basiliximab and steroids	Arm B: Basiliximab and rapid steroid withdrawal	Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal	Intention-to-treat / Safety
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	206[5]	189[6]	192[7]	587[8]
Units: Rejections				
Yes	34	28	27	89
No	172	161	165	498

Notes:

[5] - IIT / Safety population

[6] - IIT / Safety population

[7] - IIT / Safety population

[8] - IIT / Safety population

Statistical analyses

Statistical analysis title	Biopsy proven rejection rates (incl. borderline)

Statistical analysis description:

Analysis of Efficacy: Biopsy proven rejection rates (including borderline) (additional analysis)

Comparison groups	Arm A: Basiliximab and steroids v Arm C: Rabbit ATG induction therapy + rapid steroid withdrawal v Intention-to-treat / Safety
Number of subjects included in analysis	985
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.578
Method	Fisher exact

Statistical analysis title	Biopsy proven rejection rates (incl. borderline)
Statistical analysis description:	
Analysis of Efficacy: Biopsy proven rejection rates (including borderline) (additional analysis)	
Comparison groups	Arm A: Basiliximab and steroids v Arm B: Basiliximab and rapid steroid withdrawal v Intention-to-treat / Safety
Number of subjects included in analysis	982
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Date of Randomization to End of Treatment

Adverse event reporting additional description:

Safety was evaluated by clinical assessment including vital signs and laboratory analyses designed to determine the incidence of all adverse and serious adverse events, infections, malignancies, and death throughout the study. Documentation of clinical signs and laboratory data were obtained at baseline, day 7, day 14, months 1, 3, 6, 9, and 12.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	TRT Group A
Reporting group description: -	
Reporting group title	TRT Group B
Reporting group description: -	
Reporting group title	TRT Group C

Reporting group description: -

Serious adverse events	TRT Group A	TRT Group B	TRT Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 206 (57.28%)	129 / 189 (68.25%)	111 / 192 (57.81%)
number of deaths (all causes)	8	3	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	5 / 206 (2.43%)	0 / 189 (0.00%)	4 / 192 (2.08%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Vascular disorders			
Vascular disorders			
subjects affected / exposed	17 / 206 (8.25%)	7 / 189 (3.70%)	8 / 192 (4.17%)
occurrences causally related to treatment / all	2 / 19	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Surgical procedures			

subjects affected / exposed	3 / 206 (1.46%)	6 / 189 (3.17%)	3 / 192 (1.56%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
General disorders and administration site conditions			
General disorders			
subjects affected / exposed	15 / 206 (7.28%)	8 / 189 (4.23%)	8 / 192 (4.17%)
occurrences causally related to treatment / all	3 / 15	1 / 8	1 / 9
deaths causally related to treatment / all	0 / 2	0 / 0	1 / 3
Immune system disorders			
Immune system disorder			
subjects affected / exposed	13 / 206 (6.31%)	18 / 189 (9.52%)	9 / 192 (4.69%)
occurrences causally related to treatment / all	6 / 13	8 / 18	2 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Social problem			
subjects affected / exposed	0 / 206 (0.00%)	1 / 189 (0.53%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Reproductive tract disorder			
subjects affected / exposed	4 / 206 (1.94%)	4 / 189 (2.12%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	7 / 206 (3.40%)	5 / 189 (2.65%)	4 / 192 (2.08%)
occurrences causally related to treatment / all	0 / 7	2 / 5	2 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Psychiatric disorders			
Psychiatric symptom			
subjects affected / exposed	1 / 206 (0.49%)	7 / 189 (3.70%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Investigation			
subjects affected / exposed	29 / 206 (14.08%)	37 / 189 (19.58%)	30 / 192 (15.63%)
occurrences causally related to treatment / all	4 / 39	17 / 25	9 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Poisoning			
subjects affected / exposed	17 / 206 (8.25%)	21 / 189 (11.11%)	24 / 192 (12.50%)
occurrences causally related to treatment / all	3 / 19	5 / 24	5 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	15 / 206 (7.28%)	9 / 189 (4.76%)	11 / 192 (5.73%)
occurrences causally related to treatment / all	2 / 16	0 / 9	1 / 12
deaths causally related to treatment / all	1 / 2	0 / 2	0 / 2
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	4 / 206 (1.94%)	3 / 189 (1.59%)	3 / 192 (1.56%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Blood and lymphatic system disorders			
Blood disorder			
subjects affected / exposed	4 / 206 (1.94%)	8 / 189 (4.23%)	7 / 192 (3.65%)
occurrences causally related to treatment / all	4 / 4	6 / 8	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorder	Additional description: From Date of Randomization to End of Treatment		
subjects affected / exposed	13 / 206 (6.31%)	20 / 189 (10.58%)	10 / 192 (5.21%)
occurrences causally related to treatment / all	5 / 15	8 / 21	3 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	3 / 206 (1.46%)	3 / 189 (1.59%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Skin disorder			
subjects affected / exposed	1 / 206 (0.49%)	0 / 189 (0.00%)	0 / 192 (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
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	29 / 206 (14.08%)	24 / 189 (12.70%)	20 / 192 (10.42%)
occurrences causally related to treatment / all	8 / 39	5 / 25	6 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	1 / 206 (0.49%)	0 / 189 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection	Additional description: From Date of Randomization to End of Treatment		
subjects affected / exposed	36 / 206 (17.48%)	35 / 189 (18.52%)	31 / 192 (16.15%)
occurrences causally related to treatment / all	17 / 48	22 / 47	28 / 38
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metabolism and nutrition disorders			
Metabolic disorder	Additional description: From Date of Randomization to End of Treatment		
subjects affected / exposed	5 / 206 (2.43%)	5 / 189 (2.65%)	5 / 192 (2.60%)
occurrences causally related to treatment / all	5 / 5	2 / 6	1 / 5
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TRT Group A	TRT Group B	TRT Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	196 / 206 (95.15%)	185 / 189 (97.88%)	183 / 192 (95.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	14 / 206 (6.80%)	8 / 189 (4.23%)	12 / 192 (6.25%)
occurrences (all)	15	14	14
Vascular disorders			

Vascular			
subjects affected / exposed	65 / 206 (31.55%)	58 / 189 (30.69%)	48 / 192 (25.00%)
occurrences (all)	93	82	68
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	12 / 206 (5.83%)	11 / 189 (5.82%)	10 / 192 (5.21%)
occurrences (all)	13	12	11
General disorders and administration site conditions			
General symptom			
subjects affected / exposed	81 / 206 (39.32%)	66 / 189 (34.92%)	55 / 192 (28.65%)
occurrences (all)	120	106	88
Immune system disorders			
Immune system disorder			
subjects affected / exposed	18 / 206 (8.74%)	23 / 189 (12.17%)	15 / 192 (7.81%)
occurrences (all)	18	23	15
Reproductive system and breast disorders			
Reproductive tract disorder			
subjects affected / exposed	22 / 206 (10.68%)	15 / 189 (7.94%)	14 / 192 (7.29%)
occurrences (all)	23	16	17
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	32 / 206 (15.53%)	39 / 189 (20.63%)	38 / 192 (19.79%)
occurrences (all)	54	56	56
Psychiatric disorders			
Psychiatric symptom			
subjects affected / exposed	54 / 206 (26.21%)	67 / 189 (35.45%)	51 / 192 (26.56%)
occurrences (all)	65	82	72
Investigations			
Investigation			
subjects affected / exposed	84 / 206 (40.78%)	97 / 189 (51.32%)	90 / 192 (46.88%)
occurrences (all)	110	134	132
Injury, poisoning and procedural complications			
Poisoning			
subjects affected / exposed	91 / 206 (44.17%)	91 / 189 (48.15%)	90 / 192 (46.88%)
occurrences (all)	142	145	139
Cardiac disorders			

Cardiac disorder			
subjects affected / exposed	38 / 206 (18.45%)	26 / 189 (13.76%)	33 / 192 (17.19%)
occurrences (all)	47	38	42
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	53 / 206 (25.73%)	43 / 189 (22.75%)	50 / 192 (26.04%)
occurrences (all)	67	57	66
Blood and lymphatic system disorders			
Lymphatic disorder			
subjects affected / exposed	72 / 206 (34.95%)	86 / 189 (45.50%)	94 / 192 (48.96%)
occurrences (all)	104	115	156
All blood systems			
subjects affected / exposed	196 / 206 (95.15%)	185 / 189 (97.88%)	183 / 192 (95.31%)
occurrences (all)	1838	1834	5371
Eye disorders			
Eye disorder			
subjects affected / exposed	10 / 206 (4.85%)	11 / 189 (5.82%)	8 / 192 (4.17%)
occurrences (all)	10	12	8
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	104 / 206 (50.49%)	113 / 189 (59.79%)	100 / 192 (52.08%)
occurrences (all)	245	244	228
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	31 / 206 (15.05%)	40 / 189 (21.16%)	21 / 192 (10.94%)
occurrences (all)	40	56	30
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	87 / 206 (42.23%)	65 / 189 (34.39%)	68 / 192 (35.42%)
occurrences (all)	167	131	111
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	38 / 206 (18.45%)	48 / 189 (25.40%)	43 / 192 (22.40%)
occurrences (all)	62	66	58
Infections and infestations			
Infection			
subjects affected / exposed	98 / 206 (47.57%)	82 / 189 (43.39%)	78 / 192 (40.63%)
occurrences (all)	148	130	115

Metabolism and nutrition disorders Metabolic disorder subjects affected / exposed occurrences (all)	110 / 206 (53.40%) 248	103 / 189 (54.50%) 252	95 / 192 (49.48%) 237

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2008	Amendment No. 3 (D3), Version 1.0, dated 30 Sep 2008 Additional sites
25 August 2011	Study Protocol, Version 4.0, dated 25 Aug 2011 Change of Sponsor

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27871759