



## Clinical trial results:

**A randomized, prospective, multicenter trial to compare the effect on chronic allograft nephropathy prevention of mycophenolate mofetil versus azathioprine as the sole immunosuppressive therapy for kidney transplant recipients**

### Summary

EudraCT number	2006-005604-14
Trial protocol	IT
Global end of trial date	23 August 2016

### Results information

Result version number	v1 (current)
This version publication date	25 July 2019
First version publication date	25 July 2019

### Trial information

#### Trial identification

Sponsor protocol code	ATHENA Study
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00494741
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
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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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	31 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2016
Global end of trial reached?	Yes
Global end of trial date	23 August 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The study primarily compare the incidence of biopsy-proven CAN three years post-transplant in kidney recipients randomly allocated to MMF or AZA, after induction therapy with basiliximab and low-dose RATG, and sequential steroid and CsA withdrawal. Secondly, the study compare acute rejections after CsA withdrawal, long-term patient and graft survival, and graft function and prevalence/severity of CAN at study end.

Protection of trial subjects:

This study was conducted in conformance with Declaration of Helsinki, Good Clinical Practice standards and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research and privacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Italy: 233
Worldwide total number of subjects	233
EEA total number of subjects	233

Notes:

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**Subjects enrolled per age group**

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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)	195
From 65 to 84 years	38

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited between July 4th, 2007 and July 6th, 2012, and followed up to August 23th, 2016.

### Pre-assignment

Screening details:

Patients were identified among the subjects who were referred to the six Italian transplant centers involved in the trial and selected to receive the first single or double kidney transplant according to standardized clinical criteria

### Period 1

Period 1 title	Treatment period (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>	Azathioprine

Arm description:

Patients randomized in this group will receive 75 mg of AZA per os (or 125 mg if body weight > 75 kg) once a day starting on the day of transplant. AZA dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate.

Arm type	Experimental
Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomized in this group will receive 75 mg of AZA per os (or 125 mg if body weight > 75 kg) once a day starting on the day of transplant. AZA dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate

<b>Arm title</b>	Mycophenolate Mofetil
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Arm description:

Patients randomized in this group will receive 750 mg of MMF per os twice a day starting on the day of transplant. MMF dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate

Arm type	Experimental
Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomized in this group will receive 750 mg of MMF per os twice a day starting on the day of transplant. MMF dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate.

<b>Number of subjects in period 1</b>	Azathioprine	Mycophenolate Mofetil
Started	114	119
Completed	95	100
Not completed	19	19
Adverse event, serious fatal	7	3
Consent withdrawn by subject	1	3
Participating center withdrawal	4	-
Adverse event, non-fatal	7	8
Lost to follow-up	-	2
Participating Centre withdrawal	-	1
Protocol deviation	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Azathioprine
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Reporting group description:

Patients randomized in this group will receive 75 mg of AZA per os (or 125 mg if body weight > 75 kg) once a day starting on the day of transplant. AZA dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate.

Reporting group title	Mycophenolate Mofetil
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Reporting group description:

Patients randomized in this group will receive 750 mg of MMF per os twice a day starting on the day of transplant. MMF dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate

Reporting group values	Azathioprine	Mycophenolate Mofetil	Total
Number of subjects	114	119	233
Age categorical			
Units: Subjects			
Adults (18-64 years)	96	99	195
From 65-84 years	18	20	38
Age continuous			
Units: years			
arithmetic mean	52.5	52.4	
standard deviation	± 12.5	± 12.5	-
Gender categorical			
Units: Subjects			
Female	30	41	71
Male	84	78	162
Single/Double kidney graft			
Units: Subjects			
Single	105	108	213
Double	9	11	20
Hypertension before trasplant			
Units: Subjects			
Presence	41	35	76
Absence	73	84	157
Pannel reactive antibody (PRA)			
Units: Subjects			
PRA>20%	2	0	2
PRA<20%	112	119	231
Primary cause of renal failure			
Units: Subjects			
Diabetes mellitus	2	2	4
Glomerulonephritis	24	28	52
Hypertension, renovascular disease	10	8	18
Polycystic kidney disease	27	23	50
Pyelonephritis/Interstitial nephritis	4	1	5
Systemic disease	2	4	6
Urinary tract alteration	5	10	15

Other	13	23	36
Uncertain	27	20	47
Donors gender			
Units: Subjects			
Female	57	56	113
Male	57	63	120
HLA A mismatches			
Units: Subjects			
HLA A 0	18	20	38
HLA A 1	64	60	124
HLA A 2	32	39	71
HLA B mismatches			
Units: Subjects			
HLA B 0	16	14	30
HLA B 1	46	54	100
HLA B 2	52	51	103
HLA DR mismatches			
Units: Subjects			
HLA DR 0	14	17	31
HLA DR 1	62	60	122
HLA DR 2	38	42	80
Weight			
Units: Kg			
arithmetic mean	71.6	68.1	
standard deviation	± 13.2	± 14.0	-
BMI			
Units: Kg/m2			
arithmetic mean	24.4	23.9	
standard deviation	± 3.8	± 4.1	-
Systolic blood pressure			
Units: mmHg			
arithmetic mean	137.2	139	
standard deviation	± 21.6	± 27.5	-
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	81.6	81.9	
standard deviation	± 11.6	± 13.3	-
Duration of Previous dialysis			
Units: months			
arithmetic mean	51.6	55.0	
standard deviation	± 28.4	± 39.0	-
Age of donors			
Units: Year			
arithmetic mean	50.6	51.7	
standard deviation	± 14.9	± 14.9	-
Weight of donors			
Units: Kg			
arithmetic mean	71.3	72.9	
standard deviation	± 17.7	± 15.8	-

## End points

### End points reporting groups

Reporting group title	Azathioprine
Reporting group description: Patients randomized in this group will receive 75 mg of AZA per os (or 125 mg if body weight > 75 kg) once a day starting on the day of transplant. AZA dose will be reduced in case of white blood cell count lower than 2,000/mm <sup>3</sup> and whenever deemed clinically appropriate.	
Reporting group title	Mycophenolate Mofetil
Reporting group description: Patients randomized in this group will receive 750 mg of MMF per os twice a day starting on the day of transplant. MMF dose will be reduced in case of white blood cell count lower than 2,000/mm <sup>3</sup> and whenever deemed clinically appropriate	

### Primary: The incidence of Chronic Allograft Nephropathy (CAN)

End point title	The incidence of Chronic Allograft Nephropathy (CAN)
End point description: To compare the incidence of CAN 3 years post-transplantation in patients receiving induction therapy with basiliximab and low-dose RATG and randomized to maintenance immunosuppression with low-dose MMF or AZA monotherapy. Due to organizational problem CAN events have been evaluated with the graft biopsy performed between 24 month and 50 month post transplantation.	
End point type	Primary
End point timeframe: To compare the incidence of CAN 3 years post-transplantation in patients receiving induction therapy with basiliximab and low-dose RATG and randomized to maintenance immunosuppression with low-dose MMF or AZA monotherapy.	

End point values	Azathioprine	Mycophenolate Mofetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73 <sup>[1]</sup>	72 <sup>[2]</sup>		
Units: Event	37	40		

Notes:

[1] - 41 patient didn't have biopsy data to evaluate the primary endpoint due to organizational problems

[2] - 47 patient didn't have biopsy data to evaluate the primary endpoint due to organizational problems

### Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: Comparison of Chronic Allograft Nephropathy incidences between patient treated with Azathioprine or Micofenolate at 3 year post transplantation . Due to organizational problem CAN events have been evaluated with the graft biopsy performed between 24 month and 50 month post transplantation.	
Comparison groups	Mycophenolate Mofetil v Azathioprine



Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.3304 <sup>[4]</sup>
Method	Logrank

Notes:

[3] - Survival analysis

[4] - Wilcoxon p=0.3862

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events will be reported during whole study up to 30 days after last dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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### Reporting groups

Reporting group title	Azathioprine
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Reporting group description:

Patients randomized in this group will receive 75 mg of AZA per os (or 125 mg if body weight > 75 kg) once a day starting on the day of transplant. AZA dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate.

Reporting group title	Mycophenolate Mofetil
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Reporting group description:

Patients randomized in this group will receive 750 mg of MMF per os twice a day starting on the day of transplant. MMF dose will be reduced in case of white blood cell count lower than 2,000/mm3 and whenever deemed clinically appropriate

Serious adverse events	Azathioprine	Mycophenolate Mofetil	
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 114 (82.46%)	96 / 119 (80.67%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	3 / 114 (2.63%)	5 / 119 (4.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm bladder			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm stomach			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm hematologic			

subjects affected / exposed	2 / 114 (1.75%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm kidney			
subjects affected / exposed	6 / 114 (5.26%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm prostate			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Other disease			
subjects affected / exposed	27 / 114 (23.68%)	18 / 119 (15.13%)	
occurrences causally related to treatment / all	0 / 30	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	18 / 114 (15.79%)	13 / 119 (10.92%)	
occurrences causally related to treatment / all	0 / 20	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Mood disorder			
subjects affected / exposed	2 / 114 (1.75%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Surgical event			
subjects affected / exposed	10 / 114 (8.77%)	9 / 119 (7.56%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac and vascular			

subjects affected / exposed	17 / 114 (14.91%)	20 / 119 (16.81%)	
occurrences causally related to treatment / all	0 / 26	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 3	
Nervous system disorders			
Neurologic disorder			
subjects affected / exposed	1 / 114 (0.88%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 114 (1.75%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematologic disease			
subjects affected / exposed	7 / 114 (6.14%)	7 / 119 (5.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Liver and gastrointestinal disease			
subjects affected / exposed	17 / 114 (14.91%)	21 / 119 (17.65%)	
occurrences causally related to treatment / all	0 / 18	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral disorder			
subjects affected / exposed	2 / 114 (1.75%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Transplant rejection			
Additional description: Acute cellular and/or humoral rejection according to Banff 09			

subjects affected / exposed	50 / 114 (43.86%)	53 / 119 (44.54%)	
occurrences causally related to treatment / all	0 / 52	0 / 55	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed graft function			
subjects affected / exposed	10 / 114 (8.77%)	6 / 119 (5.04%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary disease recurrence			
subjects affected / exposed	1 / 114 (0.88%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft dysfunction			
subjects affected / exposed	10 / 114 (8.77%)	13 / 119 (10.92%)	
occurrences causally related to treatment / all	0 / 15	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Native kidney cyst infection			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urological disorder			
subjects affected / exposed	23 / 114 (20.18%)	22 / 119 (18.49%)	
occurrences causally related to treatment / all	0 / 21	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Severe hyperparathyroidism			
subjects affected / exposed	20 / 114 (17.54%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
parathyroid adenoma			
subjects affected / exposed	1 / 114 (0.88%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Skin, subcutaneous, musculoskeletal, and trauma			
subjects affected / exposed	3 / 114 (2.63%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection disease			
subjects affected / exposed	34 / 114 (29.82%)	23 / 119 (19.33%)	
occurrences causally related to treatment / all	0 / 49	0 / 42	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	2 / 114 (1.75%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Azathioprine	Mycophenolate Mofetil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 114 (99.12%)	114 / 119 (95.80%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Bening nodule			
subjects affected / exposed	1 / 114 (0.88%)	1 / 119 (0.84%)	
occurrences (all)	1	1	
Bening thyroid nodule			
subjects affected / exposed	1 / 114 (0.88%)	0 / 119 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Surgical intervention			
subjects affected / exposed	10 / 114 (8.77%)	9 / 119 (7.56%)	
occurrences (all)	12	12	
General disorders and administration site conditions			
Allergy			
subjects affected / exposed	1 / 114 (0.88%)	1 / 119 (0.84%)	
occurrences (all)	1	1	

Oral disorder subjects affected / exposed occurrences (all)	11 / 114 (9.65%) 11	14 / 119 (11.76%) 16	
Other Disease subjects affected / exposed occurrences (all)	78 / 114 (68.42%) 168	74 / 119 (62.18%) 142	
Reproductive system and breast disorders Urological disorder subjects affected / exposed occurrences (all)	30 / 114 (26.32%) 43	42 / 119 (35.29%) 60	
Respiratory, thoracic and mediastinal disorders Respiratory disease subjects affected / exposed occurrences (all)	34 / 114 (29.82%) 49	31 / 119 (26.05%) 48	
Psychiatric disorders Mood disorder subjects affected / exposed occurrences (all)	20 / 114 (17.54%) 22	24 / 119 (20.17%) 25	
Cardiac disorders Cardiac and vascular disease subjects affected / exposed occurrences (all)	47 / 114 (41.23%) 76	51 / 119 (42.86%) 74	
Nervous system disorders Neurologic disorder subjects affected / exposed occurrences (all)	25 / 114 (21.93%) 32	25 / 119 (21.01%) 30	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Hematologic disorder subjects affected / exposed occurrences (all)  Leukopenia subjects affected / exposed occurrences (all)  Thrombocytopenia	55 / 114 (48.25%) 71  22 / 114 (19.30%) 22  68 / 114 (59.65%) 82	45 / 119 (37.82%) 55  20 / 119 (16.81%) 25  46 / 119 (38.66%) 64	

subjects affected / exposed occurrences (all)	24 / 114 (21.05%) 28	13 / 119 (10.92%) 13	
Eye disorders			
Relapse of ocular neoplasia subjects affected / exposed occurrences (all)	0 / 114 (0.00%) 0	1 / 119 (0.84%) 1	
Ocular disease subjects affected / exposed occurrences (all)	17 / 114 (14.91%) 24	14 / 119 (11.76%) 18	
Gastrointestinal disorders			
Liver and gastrointestinal disease subjects affected / exposed occurrences (all)	59 / 114 (51.75%) 114	61 / 119 (51.26%) 104	
Skin and subcutaneous tissue disorders			
Skin disease subjects affected / exposed occurrences (all)	38 / 114 (33.33%) 57	36 / 119 (30.25%) 46	
Renal and urinary disorders			
Chronic allograft nephropathy subjects affected / exposed occurrences (all)	21 / 114 (18.42%) 21	32 / 119 (26.89%) 32	
Delayed graft function subjects affected / exposed occurrences (all)	15 / 114 (13.16%) 15	10 / 119 (8.40%) 10	
Primary renal disease recurrence subjects affected / exposed occurrences (all)	3 / 114 (2.63%) 3	0 / 119 (0.00%) 0	
Graft dysfunction subjects affected / exposed occurrences (all)	24 / 114 (21.05%) 30	28 / 119 (23.53%) 34	
End stage renal disease subjects affected / exposed occurrences (all)	6 / 114 (5.26%) 6	4 / 119 (3.36%) 4	
Urinary disorder subjects affected / exposed occurrences (all)	5 / 114 (4.39%) 5	2 / 119 (1.68%) 2	
Endocrine disorders			



Hyperparathyroidism secondary subjects affected / exposed occurrences (all)	19 / 114 (16.67%) 19	22 / 119 (18.49%) 24	
Infections and infestations Infection subjects affected / exposed occurrences (all)	80 / 114 (70.18%) 184	84 / 119 (70.59%) 183	
Metabolism and nutrition disorders Metabolic disorder subjects affected / exposed occurrences (all)	97 / 114 (85.09%) 349	100 / 119 (84.03%) 339	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2007	Study protocol amendment n. 1 Admitted the enrollment of patient >60 years old Excluded the patient receiving a transplant from living donors. Added the histological evaluation at baseline Better detailed the criteria for the histological evaluation at the first year Detailed the CsA tapering, the patient monitoring during follow up period and stopping rules. Better defined the safety interim analysis
15 October 2007	Study protocol amendment n. 2 Modified the induction therapy with the introduction of methylprednisolone at 500, 200, 125 mg the three days after the transplant and modified the cyclosporine dosage during the first year to reduce the risk of acute rejection. Modified the collection of the biochemical parameters according to the standard clinical practice
08 August 2008	Study protocol amendment n. 3 Modified induction therapy with basiliximab (two 20 mg injections: the first one pre-operatively, the second one 4 days post-transplant) plus RATG lowdose (0.5 mg/kg/day for 7 days, starting pre-operatively on the day of transplant). Patients also received intravenous methylprednisolone on day 0 (500 mg), day 1 (250 mg) and day 2 (125 mg) and oral prednisone on day 3 (75 mg), 4 (50 mg), 5 (25 mg) and 6 (25 mg). Thereafter, patients were free of steroid therapy.
31 March 2009	Study protocol amendment n. 4 - Included patients receiving double kidney transplant from deceased donors
06 October 2011	Study protocol amendment n. 5 The original schema applied for the progressive reduction of cyclosporin and complete suspension in 20 weeks (starting from a kidney biopsy scheduled for a one-year post-transplant protocol) was changed due to safety reasons. In order to standardize CsA tapering and achieving CsA withdrawal over an homogeneous follow-up period, patients will reduce the initial CsA dose by about 10% every 4 weeks. By this approach, 50% tapering should be achieved in 24 weeks. After additional 6 months at 50% of the initial CsA dose in addition to MMF or azathioprine as maintenance immunosuppressive therapy, should no rejection episodes occur (second year biopsy), a further progressive tapering of CsA dose will be attempted up to complete CsA withdrawal. Tapering will be scheduled as above and the initial CsA dose (at time of 1st graft biopsy) will be reduced by about 10% every 4 weeks. Thus, complete CsA withdrawal will be achieved 18 months after starting the initial CsA tapering, i.e at 29-30 months post-transplantation.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported