



## 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 |
|-----------------------|--------------|

#### 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                                                                                                               |
| Sponsor organisation address | V. G. B. Camozzi, 3, Ranica / Bergamo, Italy, 24010                                                                                                                 |
| Public contact               | Piero Ruggerenti, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, V. G. B. Camozzi, 3, 24010 Ranica / Bergamo, 0039 03545351, piero.ruggerenti@marionegri.it |
| Scientific contact           | Piero Ruggerenti, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, V. G. B. Camozzi, 3, 24010 Ranica / Bergamo, 0039 03545351, piero.ruggerenti@marionegri.it |

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 |
|-------------------|---|

## 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 |
|------------------|-----------------------|

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<br>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 |
|-----------------------|--------------|

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 |
|-----------------------|-----------------------|

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:<br>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:<br>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:<br>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.<br>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:<br>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:<br>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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

### 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/mm3 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/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<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                 | 11 / 114 (9.65%)<br>11                                                                | 14 / 119 (11.76%)<br>16                                                               |  |
| Other Disease<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                 | 78 / 114 (68.42%)<br>168                                                              | 74 / 119 (62.18%)<br>142                                                              |  |
| Reproductive system and breast disorders<br>Urological disorder<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                               | 30 / 114 (26.32%)<br>43                                                               | 42 / 119 (35.29%)<br>60                                                               |  |
| Respiratory, thoracic and mediastinal disorders<br>Respiratory disease<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                        | 34 / 114 (29.82%)<br>49                                                               | 31 / 119 (26.05%)<br>48                                                               |  |
| Psychiatric disorders<br>Mood disorder<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                        | 20 / 114 (17.54%)<br>22                                                               | 24 / 119 (20.17%)<br>25                                                               |  |
| Cardiac disorders<br>Cardiac and vascular disease<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                             | 47 / 114 (41.23%)<br>76                                                               | 51 / 119 (42.86%)<br>74                                                               |  |
| Nervous system disorders<br>Neurologic disorder<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                               | 25 / 114 (21.93%)<br>32                                                               | 25 / 119 (21.01%)<br>30                                                               |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hematologic disorder<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia | 55 / 114 (48.25%)<br>71<br><br>22 / 114 (19.30%)<br>22<br><br>68 / 114 (59.65%)<br>82 | 45 / 119 (37.82%)<br>55<br><br>20 / 119 (16.81%)<br>25<br><br>46 / 119 (38.66%)<br>64 |  |

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

|                                                                                                              |                          |                           |  |
|--------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------|--|
| Hyperparathyroidism secondary<br>subjects affected / exposed<br>occurrences (all)                            | 19 / 114 (16.67%)<br>19  | 22 / 119 (18.49%)<br>24   |  |
| Infections and infestations<br>Infection<br>subjects affected / exposed<br>occurrences (all)                 | 80 / 114 (70.18%)<br>184 | 84 / 119 (70.59%)<br>183  |  |
| Metabolism and nutrition disorders<br>Metabolic disorder<br>subjects affected / exposed<br>occurrences (all) | 97 / 114 (85.09%)<br>349 | 100 / 119 (84.03%)<br>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<br>Admitted the enrollment of patient >60 years old<br>Excluded the patient receiving a transplant from living donors.<br>Added the histological evaluation at baseline<br>Better detailed the criteria for the histological evaluation at the first year<br>Detailed the CsA tapering, the patient monitoring during follow up period and stopping rules.<br>Better defined the safety interim analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 15 October 2007 | Study protocol amendment n. 2<br>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.<br>Modified the collection of the biochemical parameters according to the standard clinical practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 08 August 2008  | Study protocol amendment n. 3<br>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<br>- Included patients receiving double kidney transplant from deceased donors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 06 October 2011 | Study protocol amendment n. 5<br>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.<br>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