



## 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 |
| Scientific contact           | Prof. Dr. Oliver Thomusch, Medical Center – University of Freiburg, +49 76127028060, oliver.thomusch@uniklinik-freiburg.de |

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 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 587 |
| Worldwide total number of subjects   | 587          |
| EEA total number of subjects         | 587          |

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)                      | 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 <sup>[1]</sup> |
| 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

|   |  |
|---|--|
| <b>Arm title</b>  | 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

|  |   |
|--|---|
| <b>Arm title</b>   | 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  |

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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/ $\mu$ l)

|  |                    |
|--|--------------------|
| 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:<br>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:<br>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:<br>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<br>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<br>Units: Subjects  |                                 |   |  |
| Female   | 65                              | 67  | 68   |
| Male   | 141                             | 122   | 124  |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 587   |  |  |
| Age categorical<br>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:<br>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:<br>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:<br>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:<br>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:<br>Biopsy proven rejection rates (excluding borderline) (additional analysis) |   |
| End point type   | Primary   |
| End point timeframe:<br>12 months  |   |

| End point values            | Arm A:<br>Basiliximab<br>and steroids | Arm B:<br>Basiliximab<br>and rapid<br>steroid<br>withdrawal | Arm C: Rabbit<br>ATG induction<br>therapy +<br>rapid steroid<br>withdrawal | Intention-to-<br>treat / Safety |
|-----------------------------|---------------------------------------|---|--|---------------------------------|
| Subject group type          | Reporting group                       | Reporting group   | Reporting group  | Subject analysis set            |
| Number of subjects analysed | 206 <sup>[1]</sup>                    | 189 <sup>[2]</sup>  | 192 <sup>[3]</sup>   | 587 <sup>[4]</sup>              |
| 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:<br>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   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Primary efficacy analysis BPAR rate: group B vs C  |
| Statistical analysis description:<br>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:<br>Within the first year after renal transplantation |  |

| End point values                            | Arm A:<br>Basiliximab<br>and steroids | Arm B:<br>Basiliximab<br>and rapid<br>steroid<br>withdrawal | Arm C: Rabbit<br>ATG induction<br>therapy +<br>rapid steroid<br>withdrawal | Intention-to-<br>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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>              | 189 <sup>[6]</sup>                              | 192 <sup>[7]</sup>   | 587 <sup>[8]</sup>          |
| 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

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | 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   |

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

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

|                                    |                    |                    |                   |
|------------------------------------|--------------------|--------------------|-------------------|
| Metabolism and nutrition disorders |                    |                    |                   |
| Metabolic disorder                 |                    |                    |                   |
| subjects affected / exposed        | 110 / 206 (53.40%) | 103 / 189 (54.50%) | 95 / 192 (49.48%) |
| occurrences (all)                  | 248                | 252                | 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<br>Additional sites |
| 25 August 2011    | Study Protocol, Version 4.0, dated 25 Aug 2011<br>Change of Sponsor      |

Notes:

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### 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:

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### Online references

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