



Clinical trial results:

A Phase II, Open-label, Multi-center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® Based Immunosuppressive Regimen, Including a Long-term Follow-up

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2010-020925-42 |
| Trial protocol | AT FR DE BE PL CZ IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|-------------|
| Result version number | v1 |
| This version publication date | 19 May 2017 |
| First version publication date | 19 May 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | PMR-EC-1206 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01294020 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Astellas Pharma Europe, Ltd |
| Sponsor organisation address | 2000 Hillswood Drive, Chertsey Surrey, United Kingdom, KT16 0RS |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Europe, Ltd, astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Europe, Ltd, astellas.resultsdisclosure@astellas.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 28 October 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|------------------------------|----|
| Global end of trial reached? | No |
|------------------------------|----|

Notes:

General information about the trial

Main objective of the trial:

To compare the steady state area under the plasma concentration-time curve from time 0 to time 24 hours (AUC0-24h) of tacrolimus for tacrolimus prolonged release (Advagraf) with that of tacrolimus (Prograf) in stable pediatric allograft recipients after 1:1 (mg:mg) conversion from Prograf to Advagraf.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

This study is composed of 3 parts: Part A (Pharmacokinetics), Part B (Long-term follow-up) and Part C (Continuation of long-term follow-up until participants discontinued treatment or received the approved treatment). After enrollment, participants entered a 30-day screening period in Part A of the study during which time they were maintained on their routine twice daily tacrolimus (commercial Prograf) based immunosuppressive regimen, as determined by the Investigator and as supplied by the local hospital pharmacy.

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 25 May 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 10 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | France: 22 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Poland: 28 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Worldwide total number of subjects | 81 |
| EEA total number of subjects | 81 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 35 |
| Adolescents (12-17 years) | 46 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Children aged 5 years to 16 years of age were enrolled in sites in 7 countries: Belgium, Czech Republic, Germany, France, Italy, Poland and UK for this 3-part study. Results reported in this disclosure include data from Part A and Part B of the study.

Pre-assignment

Screening details:

Stable pediatric allograft recipients (children who previously received a single organ liver, kidney, heart, lung or intestinal transplantation [≥ 6 months post-transplant]) being treated with a tacrolimus based immunosuppressive regimen (≤ 3 months) who consented to enter this study and fulfilled all the eligibility criteria were enrolled.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Part A: Pharmacokinetics |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------------------------------------|
| Arm title | Tacrolimus Prolonged Release (Part A) |
|-----------|---------------------------------------|

Arm description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A of the study.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Tacrolimus prolonged release |
| Investigational medicinal product code | FK506E |
| Other name | Advagraf, Astagraf XL, Graceptor, Prograf XL |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received tacrolimus prolonged release (strengths of 0.5 mg, 1 mg, 3 mg, 5 mg) with the same daily dose (1:1, mg:mg) after being converted from tacrolimus on day 8, with the dose maintained up to day 14 in Part A of the study. Tacrolimus prolonged release capsules were taken orally once daily only in the morning, on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal.

| | |
|--|------------|
| Investigational medicinal product name | Tacrolimus |
| Investigational medicinal product code | FK506 |
| Other name | Prograf |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received tacrolimus (strengths of 0.5 mg, 1 mg, 5 mg) with the same daily dose (1:1, mg:mg) as received during the 30-day screening period in Part A of the study. Tacrolimus capsules were taken orally twice daily, morning and evening, on an empty stomach or at least 1 hour before, or 2 to 3 hours after any meal.

| Number of subjects in period 1 | Tacrolimus Prolonged Release (Part A) |
|--|---------------------------------------|
| Started | 81 |
| Treated with study drug | 81 |
| Completed | 78 |
| Not completed | 3 |
| Adverse Event | 1 |
| Withdrawal of consent | 1 |
| Site staff could not cover the overnight visit | 1 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Part B: Long-Term Follow-up |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---------------------------------------|
| Arm title | Tacrolimus Prolonged Release (Part B) |
|------------------|---------------------------------------|

Arm description:

After Part A, participants continued to receive tacrolimus prolonged release once daily from day 15 up to the end of Part B of the study.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Tacrolimus prolonged release |
| Investigational medicinal product code | FK506E |
| Other name | Advagraf, Astagraf XL, Graceptor, Prograf XL |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants continued to receive tacrolimus prolonged release (strengths of 0.5 mg, 1 mg, 3 mg, 5 mg) with the same daily dose (1:1, mg:mg) from day 15 up to the end of Part B of the study but could be adjusted on the basis of trough drug measurement results. Tacrolimus prolonged release capsules were taken orally once daily only in the morning, on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal.

| Number of subjects in period 2 | Tacrolimus Prolonged Release (Part B) |
|--------------------------------|---------------------------------------|
| Started | 78 |
| Completed | 76 |
| Not completed | 2 |
| Adverse Event | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Tacrolimus Prolonged Release (Part A) |
|-----------------------|---------------------------------------|

Reporting group description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A of the study.

| Reporting group values | Tacrolimus Prolonged Release (Part A) | Total | |
|--------------------------|---------------------------------------|-------|--|
| Number of subjects | 81 | 81 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 5-7 years | 11 | 11 | |
| 8-10 years | 17 | 17 | |
| 11-13 years | 31 | 31 | |
| 14-16 years | 22 | 22 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 11.5 | | |
| standard deviation | ± 2.87 | - | |
| Gender categorical | | | |
| Units: | | | |
| Male | 47 | 47 | |
| Female | 34 | 34 | |
| Type of Organ Transplant | | | |
| Units: Subjects | | | |
| Kidney | 48 | 48 | |
| Liver | 31 | 31 | |
| Heart | 2 | 2 | |
| Other (Lung, Intestine) | 0 | 0 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Tacrolimus Prolonged Release (Part A) |
| Reporting group description: Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7. On day 8, participants switched to tacrolimus prolonged release once daily and received treatment up to day 14 in Part A of the study. | |
| Reporting group title | Tacrolimus Prolonged Release (Part B) |
| Reporting group description: After Part A, participants continued to receive tacrolimus prolonged release once daily from day 15 up to the end of Part B of the study. | |
| Subject analysis set title | Tacrolimus (Part A) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the pharmacokinetic analysis set who received tacrolimus twice daily on day 1 up to day 7 in Part A of the study. | |
| Subject analysis set title | Tacrolimus Prolonged Release (Part A) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the pharmacokinetic analysis set who received tacrolimus prolonged release once daily from day 8 up to day 14 in Part A of the study. | |
| Subject analysis set title | Tacrolimus Prolonged Release (Part A + B) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants received tacrolimus prolonged release once daily from day 8 up to day 14 in Part A, and once daily from day 15 up to end of Part B of the study. | |

Primary: Area Under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours (AUC0-24h) for Tacrolimus and Tacrolimus Prolonged Release

| | |
|--|--|
| End point title | Area Under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours (AUC0-24h) for Tacrolimus and Tacrolimus Prolonged Release |
| End point description: The analysis population was the Pharmacokinetics Analysis Set (PKAS), which consisted of all participants who received at least 1 dose of study drug and who provided 2 complete pharmacokinetic profiles. | |
| End point type | Primary |
| End point timeframe: Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose | |

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|---|-----------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: ng*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 159.133 (\pm 32.7) | 153.8194 (\pm 29.3) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | AUC24 (steady-state systemic exposure) Comparison |
| Statistical analysis description: The comparison of pharmacokinetic (PK) parameter AUC24 between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74. | |
| Comparison groups | Tacrolimus Prolonged Release (Part A) v Tacrolimus (Part A) |
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Geometric least squares (LS) mean ratio |
| Point estimate | 96.66 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 92.31 |
| upper limit | 101.22 |

Notes:

[1] - The difference of LS means of log-transformed PK parameters between tacrolimus and tacrolimus prolonged release and its 90% CI are back-transformed to the raw scale and are expressed as percentages.

Secondary: Maximum Concentration (Cmax) of Tacrolimus and Tacrolimus Prolonged Release

| | |
|---|---|
| End point title | Maximum Concentration (Cmax) of Tacrolimus and Tacrolimus Prolonged Release |
| End point description: The analysis population was the PKAS. This PK parameter was not assessed in the evening for the tacrolimus prolonged release arm as prespecified in the protocol and is denoted as "99999." | |
| End point type | Secondary |
| End point timeframe: Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose | |

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|---|----------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |

| | | | | |
|---------|----------------------|----------------------|--|--|
| Morning | 11.792 (\pm 44.1) | 11.048 (\pm 38.9) | | |
| Evening | 8.198 (\pm 40) | 99999 (\pm 99999) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cmax Comparison |
| Statistical analysis description: | |
| The comparison of pharmacokinetic parameter Cmax between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74. | |
| Comparison groups | Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A) |
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Geometric LS mean ratio |
| Point estimate | 93.69 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 87.07 |
| upper limit | 100.81 |

Notes:

[2] - The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolimus prolonged release and its 90% CI are back-transformed to the raw scale and are expressed as percentages. Morning Cmax in tacrolimus group was used for comparison with Cmax for participants in tacrolimus prolonged release group.

Secondary: Trough Concentration (C12) for Tacrolimus

| | |
|---------------------------------------|---|
| End point title | Trough Concentration (C12) for Tacrolimus |
| End point description: | |
| The analysis population was the PKAS. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 7, 12 hours after dosing | |

| | | | | |
|---|----------------------|--|--|--|
| End point values | Tacrolimus (Part A) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 4.753 (\pm 36.2) | | | |

Statistical analyses

Secondary: Trough Concentration (C24) for Tacrolimus and Tacrolimus Prolonged Release

| | |
|---|--|
| End point title | Trough Concentration (C24) for Tacrolimus and Tacrolimus Prolonged Release |
| End point description: The analysis population was the PKAS. | |
| End point type | Secondary |
| End point timeframe: Days 7 and 14, 24 hours after dosing | |

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|---|----------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 4.955 (\pm 37.6) | 4.479 (\pm 31.7) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | C24 Comparison |
| Statistical analysis description: The comparison of pharmacokinetic parameter C24 between tacrolimus and tacrolimus prolonged release was assessed with a mixed effects model on log-transformed PK parameters with treatment, organ transplant and age (continuous variable) at baseline as fixed effects and patient as random effect. The number of participants analyzed is calculated by the system and cannot be changed; actual N=74. | |
| Comparison groups | Tacrolimus (Part A) v Tacrolimus Prolonged Release (Part A) |
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Geometric LS mean ratio |
| Point estimate | 90.39 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 85 |
| upper limit | 96.13 |

Notes:

[3] - The difference of LS means of log-transformed pharmacokinetic parameters between tacrolimus and tacrolimus prolonged release and its 90% CI are back-transformed to the raw scale and are expressed as percentages.

Secondary: Time to Attain Maximum Concentration (tmax) of Tacrolimus and Tacrolimus Prolonged Release

| | |
|-----------------|--|
| End point title | Time to Attain Maximum Concentration (tmax) of Tacrolimus and Tacrolimus Prolonged Release |
|-----------------|--|

End point description:

The analysis population was the PKAS. This PK parameter was not assessed in the evening for the tacrolimus prolonged release arm as prespecified in the protocol and is denoted as "99999."

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|-------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Morning | 1.0584 (0.9 to 6) | 1.9833 (0.917 to 24) | | |
| Evening | 3.9667 (0 to 12) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between AUC24 and C24

| | |
|-----------------|-----------------------------------|
| End point title | Correlation between AUC24 and C24 |
|-----------------|-----------------------------------|

End point description:

The analysis population was the PKAS. Only participants with available C24 and AUC24 at each visit are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 7 (for tacrolimus) and day 14 (for tacrolimus prolonged release) at predose and 1, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|--|------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: Pearson correlation coefficient | | | | |
| number (not applicable) | 0.84 | 0.89 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Acute Rejections

| | |
|-----------------|--|
| End point title | Number of Participants with Acute Rejections |
|-----------------|--|

End point description:

Rejection episodes/acute rejections were indicated by clinical and/or laboratory signs, and were classified according to their rejection specific treatment: •Spontaneously Resolving Acute Rejection: not treated with new or increased corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Sensitive Acute Rejection: treated with new or increased corticosteroid medication only and which has resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Resistant Acute Rejection: did not resolve following treatment with corticosteroids; - Resolved with further treatment: any acute rejection with an end date AND a treatment other than corticosteroid used; - Unresolved with further treatment: any acute rejection with no end date AND a treatment other than corticosteroid used; - Unresolved with no further treatment: any acute rejection with no end date AND ONLY corticosteroid treatment was used. mFAS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 54

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: participants | | | | |
| 1. Any Acute Rejections | 2 | | | |
| 1.a. Spontaneously Resolving Acute Rejection | 0 | | | |
| 1.b. Corticosteroid Sensitive Acute Rejection | 1 | | | |
| 1.c. Corticosteroid Resistant Acute Rejection | 1 | | | |
| 1.c.1 Resolved with further treatment | 1 | | | |
| 1.c.2 Unresolved with further treatment | 0 | | | |
| 1.c.3 Unresolved with no further treatment | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Biopsy Proven Acute Rejections (BPARs)

| | |
|-----------------|--|
| End point title | Number of Participants with Biopsy Proven Acute Rejections (BPARs) |
|-----------------|--|

End point description:

BPAR episodes were defined as acute rejection episodes confirmed by biopsy, and were classified according to their rejection specific treatment: •Spontaneously Resolving Acute Rejection: not treated with new or increased corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Sensitive Acute Rejection: treated with new

or increased corticosteroid medication only and which has resolved, irrespective of any tacrolimus dose changes; •Corticosteroid Resistant Acute Rejection: did not resolve following treatment with corticosteroids; - Resolved with further treatment: any acute rejection with an end date AND a treatment other than corticosteroid used; - Unresolved with further treatment: any acute rejection with no end date AND a treatment other than corticosteroid used; - Unresolved with no further treatment: any acute rejection with no end date AND ONLY corticosteroid treatment used. mFAS.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 54 | |

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: participants | | | | |
| 1. Biopsy proven acute rejections | 1 | | | |
| 1.a. Spontaneously Resolving Acute Rejection | 0 | | | |
| 1.b. Corticosteroid Sensitive Acute Rejection | 0 | | | |
| 1.c. Corticosteroid Resistant Acute Rejection | 1 | | | |
| 1.c.1 Resolved with further treatment | 1 | | | |
| 1.c.2 Unresolved with further treatment | 0 | | | |
| 1.c.3 Unresolved with no further treatment | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Biopsy Proven Acute Rejection Episodes

| | |
|--|--|
| End point title | Severity of Biopsy Proven Acute Rejection Episodes |
| End point description: | |
| <p>The severity of BPARs was categorized with specific criteria by organ: For kidney transplant participants, according to Banff '97 Diagnostic categories for renal allograft biopsies – Banff '07 update (Acute antibody-mediated rejection I, II, and III, Acute T cell mediated rejection IA, IB, IIA, IIB and III); for liver transplant participants, according to 1997 Banff Schema for grading of Liver Allograft Rejection (mild, moderate, severe or indeterminate/borderline); for heart, according to Standardized Nomenclature of the International Society of Heart and Lung Transplantation (mild, moderate, severe). The analysis population was the modified Full Analysis Set (mFAS), which consisted of all participants who received at least 1 dose of tacrolimus prolonged release study drug.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 54 | |

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: participants | | | | |
| Kidney: Antibody-mediated rejection I | 0 | | | |
| Kidney: Antibody-mediated rejection II | 1 | | | |
| Kidney:Antibody-mediated rejection III | 0 | | | |
| Kidney:T cell mediated rejection IA | 0 | | | |
| Kidney:T cell mediated rejection IB | 1 | | | |
| Kidney:T cell mediated rejection IIA | 0 | | | |
| Kidney:T cell mediated rejection IIB | 0 | | | |
| Kidney:T cell mediated rejection III | 0 | | | |
| Liver: Mild | 0 | | | |
| Liver: Moderate | 0 | | | |
| Liver: Severe | 0 | | | |
| Liver: Indeterminate or borderline | 0 | | | |
| Heart: Mild | 0 | | | |
| Heart: Moderate | 0 | | | |
| Heart: Severe | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival

| | |
|---|------------------|
| End point title | Patient survival |
| End point description: | |
| Patient survival was defined as the time from first dose of tacrolimus as study drug to the date of death from any cause. Since no participants died during the study, survival analysis was not conducted. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 54 | |

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: days | | | | |
| number (confidence interval 95%) | (to) | | | |

Notes:

[4] - There were no deaths.

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival

| | |
|-----------------|----------------|
| End point title | Graft survival |
|-----------------|----------------|

End point description:

Graft survival was defined as the time from the first dose of tacrolimus as study drug to graft loss. Graft loss was defined as retransplantation, nephrectomy (in case of kidney transplantation), death or dialysis (in case of kidney transplantation) ongoing at end of study or at discontinuation, unless superseded by follow-up information. Since no participants experienced graft loss during the study, survival analysis was not conducted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 54

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 0 ^[5] | | | |
| Units: days | | | | |
| number (confidence interval 95%) | (to) | | | |

Notes:

[5] - There were no graft losses.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Failure

| | |
|-----------------|------------------|
| End point title | Efficacy Failure |
|-----------------|------------------|

End point description:

Efficacy failure was defined as the composite of the following: death, graft loss, BPAR and unknown outcome. A participant was considered to have an unknown outcome if he/she did not have the event of interest (death, graft loss, BPAR) or did not have a study assessment prior to day 335. The analysis population was the mFAS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 54

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: participants | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (Part A)

| | |
|-----------------|---|
| End point title | Number of Participants with Adverse Events (Part A) |
|-----------------|---|

End point description:

Safety as assessed by adverse events (AEs), which included abnormalities identified during a medical test (e.g. laboratory tests, vital signs, electrocardiogram, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A serious AE (SAE) was an event resulting in death, persistent or significant disability/incapacity or congenital anomaly or birth defect, was life-threatening, required or prolonged hospitalization or was considered medically important. The analysis population was the Full Analysis Set (FAS), which consisted of all participants who received at least 1 dose of any of the study drug (tacrolimus/tacrolimus prolonged release).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of tacrolimus up to 7 days after last dose of tacrolimus prolonged release in Part A (up to 21 days)

| End point values | Tacrolimus (Part A) | Tacrolimus Prolonged Release (Part A) | | |
|---|------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 81 | 79 | | |
| Units: participants | | | | |
| AEs | 8 | 14 | | |
| Drug-related AEs | 1 | 2 | | |
| Deaths | 0 | 0 | | |
| SAEs | 0 | 0 | | |
| Drug-related SAEs | 0 | 0 | | |
| Deaths Resulting from AEs | 0 | 0 | | |
| AEs Leading to Permanent Discontinuation | 0 | 0 | | |
| Drug-related AEs Leading to Permanent Discont. | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (Part B)

| | |
|---|---|
| End point title | Number of Participants with Adverse Events (Part B) |
| End point description: | |
| Safety as assessed by adverse events (AEs), which included abnormalities identified during a medical test (e.g. laboratory tests, vital signs, electrocardiogram, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A serious AE (SAE) was an event resulting in death, persistent or significant disability/incapacity or congenital anomaly or birth defect, was life-threatening, required or prolonged hospitalization or was considered medically important. The analysis population was the mFAS. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose of tacrolimus prolonged release in Part A up to 7 days after last dose of tacrolimus prolonged release in Part B (up to 55 weeks) | |

| End point values | Tacrolimus Prolonged Release (Part A + B) | | | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: participants | | | | |
| AEs | 67 | | | |
| Drug-related AEs | 28 | | | |
| Deaths | 0 | | | |
| SAEs | 19 | | | |
| Drug-related SAEs | 10 | | | |
| Deaths Resulting from AEs | 0 | | | |
| AEs Leading to Permanent Discontinuation | 1 | | | |
| Drug-related AEs Leading to Permanent Discont. | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (tacrolimus/tacrolimus prolonged release) in Part A up to last dose of study drug (tacrolimus prolonged release) in Part B of the study

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Tacrolimus |
|-----------------------|------------|

Reporting group description:

Participants converted from their routine tacrolimus based immunosuppressive regimen to tacrolimus as a study medication twice daily on day 1 and continued to receive treatment up to day 7 in Part A of the study.

| | |
|-----------------------|------------------------------|
| Reporting group title | Tacrolimus prolonged release |
|-----------------------|------------------------------|

Reporting group description:

Participants switched to tacrolimus prolonged release once daily on day 8 and received treatment up to day 14 in Part A and continued to receive tacrolimus prolonged release once daily from day 15 up to the end of Part B of the study.

| Serious adverse events | Tacrolimus | Tacrolimus prolonged release | |
|---|----------------|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 19 / 79 (24.05%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immunosuppressant drug level increased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Expired drug administered | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Arteriovenous fistula operation | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Benign intracranial hypertension | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillar haemorrhage | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 3 / 79 (3.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superinfection bacterial | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Tacrolimus | Tacrolimus prolonged release | |
|---|---------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 8 / 81 (9.88%) | 66 / 79 (83.54%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Skin papilloma subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 4 / 79 (5.06%) 4 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Vena cava thrombosis subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Surgical and medical procedures Dermabrasion subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Enanthema subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 2 | |
| Influenza like illness | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 6 / 79 (7.59%) | |
| occurrences (all) | 0 | 8 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Cough | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 9 / 79 (11.39%) | |
| occurrences (all) | 0 | 9 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 5 / 79 (6.33%) | |
| occurrences (all) | 0 | 5 | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Abnormal behaviour subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Agitation subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Mood altered subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 2 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 6 / 79 (7.59%) 6 | |
| Blood iron decreased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 3 / 79 (3.80%) 3 | |
| Blood pressure increased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| C-reactive protein increased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Immunosuppressant drug level decreased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin D decreased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Chronic allograft nephropathy | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 2 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Drug dispensing error | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Drug dose omission | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Expired drug administered | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |

| | | | |
|---|---------------------|------------------------|--|
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Nervous system disorders | | | |
| Clonus subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Epilepsy subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 81 (2.47%) 2 | 11 / 79 (13.92%) 14 | |
| Loss of consciousness subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Migraine subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Syncope vasovagal subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 2 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 2 | |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 3 / 79 (3.80%) 3 | |
| Lymphadenitis | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 0 / 79 (0.00%) 0 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Eye disorders Chorioretinal atrophy subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Macular degeneration subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Papilloedema subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 5 / 79 (6.33%) 7 | |
| Aphthous stomatitis subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Constipation | | | |

| | | | |
|--|----------------|------------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 11 / 79 (13.92%) | |
| occurrences (all) | 0 | 17 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal motility disorder | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 3 / 79 (3.80%) | |
| occurrences (all) | 0 | 3 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 8 / 79 (10.13%) | |
| occurrences (all) | 1 | 10 | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Cold sweat | | | |

| | | |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Dermatitis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Dermatitis allergic | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Dry skin | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 1 / 79 (1.27%) |
| occurrences (all) | 1 | 1 |
| Eczema | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Ephelides | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Erythema | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Hyperhidrosis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Ingrowing nail | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) |
| occurrences (all) | 0 | 2 |
| Intertrigo | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Nail disorder | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Photodermatosis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Pityriasis rosea | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Scar pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 1 / 79 (1.27%) | |
| occurrences (all) | 1 | 1 | |
| Subcutaneous nodule | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 81 (1.23%) | 2 / 79 (2.53%) | |
| occurrences (all) | 1 | 3 | |
| Sever's disease | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Tendinous contracture | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 3 / 79 (3.80%) | |
| occurrences (all) | 0 | 4 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 4 / 79 (5.06%) | |
| occurrences (all) | 0 | 4 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 6 / 79 (7.59%) | |
| occurrences (all) | 0 | 11 | |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 4 / 79 (5.06%) | |
| occurrences (all) | 1 | 4 | |

| | | |
|-----------------------------|----------------|-----------------|
| Oropharyngeal candidiasis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Otitis externa | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Otitis media | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) |
| occurrences (all) | 0 | 2 |
| Pharyngitis | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 8 / 79 (10.13%) |
| occurrences (all) | 2 | 12 |
| Pharyngitis streptococcal | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Purulent discharge | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 2 |
| Respiratory tract infection | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 3 / 79 (3.80%) |
| occurrences (all) | 0 | 3 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 5 / 79 (6.33%) |
| occurrences (all) | 1 | 5 |
| Rotavirus infection | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Scarlet fever | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |
| Tonsillitis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 4 / 79 (5.06%) |
| occurrences (all) | 0 | 5 |
| Tracheitis | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---|---------------------|---------------------|--|
| Tracheobronchitis mycoplasmal subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 81 (1.23%) 1 | 5 / 79 (6.33%) 7 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 2 | |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 3 | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 2 | |
| Metabolism and nutrition disorders | | | |
| Anorexia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 2 / 79 (2.53%) 3 | |
| Hyperlipidaemia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 81 (0.00%) 0 | 1 / 79 (1.27%) 1 | |
| Iron deficiency | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 79 (1.27%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 79 (2.53%) | |
| occurrences (all) | 0 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 22 April 2013 | This amendment added trough levels of tacrolimus as an inclusion factor, and updated details of study administration. |
| 04 November 2013 | This amendment added the Part C extension to the study (particularly for Italy and Poland). |
| 23 April 2014 | This amendment added the Part C extension to the study (particularly for Germany and Czech Republic). |
| 01 December 2014 | The protocol was reissued to combine all the individual country-specific amendments into 1 combined Country Protocol Amendment for Italy, Poland, German and Czech Republic. |
| 28 June 2016 | This amendment added UK sites to Part C of the study to comply with a UK-specific requirement. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported