Clinical trial results:
A Multicentre, Open-label, Pharmacokinetic Study of Modigraf® (Tacrolimus Granules) in de Novo Paediatric Allograft Recipients

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-012258-19
Trial protocol	ES GB DE BE FR
Global end of trial date	03 February 2015

Results information

Result version number	v1 (current)
This version publication date	29 April 2016
First version publication date	29 April 2016

Trial information

Trial identification

Sponsor protocol code	F506-CL-0403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01371331
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: OPTION

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe, Ltd
Sponsor organisation address	2000 Hillswood Drive, Chertsey, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2015
Global end of trial reached?	Yes
Global end of trial date	03 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the pharmacokinetics (PK) of tacrolimus following oral administration of Modigraf, after the first oral dose and at steady state in pediatric participants undergoing de novo allograft transplantation.

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: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	52
EEA total number of subjects	52

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	17
Children (2-11 years)	34
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted at 10 contracted sites in a total of 6 countries including United Kingdom (UK) (1 site), Spain (3 sites), Germany (2 sites), Belgium (1 site), Poland (1 site) and France (2 sites).

Pre-assignment

Screening details:

Eligibility was determined through screening assessments; medical history, vital signs, body weight, physical examination, and clinical laboratory tests.

Period 1

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

Blinding implementation details:

As this was an open-label study, blinding was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Heart Transplant

Arm description:

This arm consisted of heart transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Arm type	Experimental
Investigational medicinal product name	Modigraf®
Investigational medicinal product code	FK506
Other name	tacrolimus granules
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Total initial daily dose of 0.3 mg/kg/day (0.15 mg/kg twice daily (BID) oral suspension) for all transplant recipients for treatment duration of 14 days (+-3 days). The first dose of 0.15 mg/kg of tacrolimus was to be administered within 24 hours (h) after reperfusion (this period may have been extended up to 5 days for heart transplant recipients. Subsequent oral tacrolimus doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and observing the following recommended whole blood trough level range of 5 to 20 ng/mL.

Arm title	Liver Transplant

Arm description:

This arm consisted of liver transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Arm type	Experimental
Investigational medicinal product name	Modigraf®
Investigational medicinal product code	FK506
Other name	tacrolimus granules
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Total initial daily dose of 0.3 mg/kg/day (0.15 mg/kg twice daily (BID) oral suspension) for all transplant recipients for treatment duration of 14 days (+-3 days). The first dose of 0.15 mg/kg of tacrolimus was to be administered within 24 hours (h) after reperfusion (this period may have been extended up to 5

days for heart transplant recipients. Subsequent oral tacrolimus doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and observing the following recommended whole blood trough level range of 5 to 20 ng/mL.

Arm title	Kidney Transplant

Arm description:

This arm consisted of kidney transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Arm type	Experimental
Investigational medicinal product name	Modigraf®
Investigational medicinal product code	FK506
Other name	tacrolimus granules
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Total initial daily dose of 0.3 mg/kg/day (0.15 mg/kg twice daily (BID) oral suspension) for all transplant recipients for treatment duration of 14 days (+-3 days). The first dose of 0.15 mg/kg of tacrolimus was to be administered within 24 hours (h) after reperfusion (this period may have been extended up to 5 days for heart transplant recipients. Subsequent oral tacrolimus doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and observing the following recommended whole blood trough level range of 5 to 20 ng/mL.

Number of subjects in period 1	Heart Transplant	Liver Transplant	Kidney Transplant
Started	17	20	15
Completed	17	17	12
Not completed	0	3	3
Withdrawal of Consent	-	-	2
Medication Therapy	-	1	-
Pharmacokinetic (PK) profile 1 not completed	-	-	1
Took prohibited medication in the trial	-	1	-
Intolerable Adverse Event (AE)	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Heart Transplant
Reporting group description:	
This arm consisted of heart transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).	
Reporting group title	Liver Transplant
Reporting group description:	
This arm consisted of liver transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).	
Reporting group title	Kidney Transplant
Reporting group description:	
This arm consisted of kidney transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).	

Reporting group values	Heart Transplant	Liver Transplant	Kidney Transplant
Number of subjects	17	20	15
Age categorical Units: Subjects			

Age continuous			
Age values were based on the Safety Analysis Set (SAF). The SAF consisted of all enrolled participants who took at least 1 dose of study medication.			
Units: years			
arithmetic mean	5.2	2.6	5.4
standard deviation	± 4.2	± 3.2	± 3
Gender categorical			
Gender values were based on the SAF.			
Units:			
Male	13	10	12
Female	4	10	3

Reporting group values	Total		
Number of subjects	52		
Age categorical Units: Subjects			

Age continuous			
Age values were based on the Safety Analysis Set (SAF). The SAF consisted of all enrolled participants who took at least 1 dose of study medication.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender values were based on the SAF.			
Units:			
Male	35		

Female	17		

End points

End points reporting groups

Reporting group title	Heart Transplant

Reporting group description:

This arm consisted of heart transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Reporting group title	Liver Transplant

Reporting group description:

This arm consisted of liver transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Reporting group title	Kidney Transplant

Reporting group description:

This arm consisted of kidney transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Subject analysis set title	Overall Participants
Subject analysis set type	Per protocol

Subject analysis set description:

All trial participants (heart, liver, kidney transplant recipients).

Primary: Area under the plasma concentration-time curve for a dosing interval (AUCtau) of tacrolimus

End point title	Area under the plasma concentration-time curve for a dosing interval (AUCtau) of tacrolimus[1]

End point description:

The study analysis population for this endpoint consisted of the pharmacokinetic (PK) analysis set (PKAS). The PKAS included all participants from the Safety Analysis Set (SAF) population who provided two complete PK profiles (on Day 1, after the first dose of tacrolimus after transplantation and at Day 7). The SAF consisted of all participants who took at least 1 dose of study medication. AUCtau was calculated using the trapezoidal rule. All analyses were performed by type of organ transplant (liver, kidney and heart transplant) and overall. In the case of a combined liver and kidney transplant the participant was counted in the liver transplant group only.

End point type	Primary

End point timeframe:

Day 1 post transplant (blood samples were collected before dosing at (0 hours) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing) and Day 7 (before dosing (0h) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing.) (+/- 7 days).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not applicable, only descriptive statistics available for this primary endpoint.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	Overall Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	14	12	38
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1	224.13 (± 114.3)	210.56 (± 84.01)	97.4 (± 36.77)	179.11 (± 99.81)
Day 7	165.17 (± 39.12)	195.08 (± 94.63)	208.32 (± 68.75)	189.81 (± 72.97)

Statistical analyses

No statistical analyses for this end point

Primary: Maximum concentration (Cmax) of tacrolimus

End point title	Maximum concentration (Cmax) of tacrolimus[2]

End point description:

The study analysis population for this endpoint consisted of the PKAS. All analyses were performed by type of organ transplant (liver, kidney and heart transplant) and overall. In the case of a combined liver and kidney transplant the participant was counted in the liver transplant group only.

End point type	Primary

End point timeframe:

Day 1 post transplant (blood samples were collected before dosing at (0 hours) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing) and Day 7 (before dosing (0h) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing.) (+/- 7 days).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not applicable, only descriptive statistics available for this primary endpoint.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	Overall Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	14	12	38
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	45.61 (± 19.55)	25.11 (± 10.78)	18.04 (± 8.1)	29.35 (± 17.55)
Day 7	32.69 (± 9.78)	30.52 (± 19.35)	36.63 (± 13.97)	33.14 (± 14.99)

Statistical analyses

No statistical analyses for this end point

Primary: Time to attain Cmax (Tmax) of tacrolimus

End point title	Time to attain Cmax (Tmax) of tacrolimus[3]

End point description:

The study analysis population for this endpoint consisted of the PKAS. All analyses were performed by type of organ transplant (liver, kidney and heart transplant) and overall. In the case of a combined liver and kidney transplant the participant was counted in the liver transplant group only.

End point type	Primary

End point timeframe:

Day 1 post transplant (blood samples were collected before dosing at (0 hours) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing) and Day 7 (before dosing (0h) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing.) (+/- 7 days).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not applicable, only descriptive statistics available for this primary endpoint.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	Overall Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	14	12	38
Units: hours (h)				
median (full range (min-max))				
Day 1	1 (0.5 to 12)	2.017 (0.98 to 8.1)	1.992 (0.97 to 4.03)	2 (0.5 to 12)
Day 7	0.775 (0.5 to 2)	1.5 (0.5 to 4)	1 (0.48 to 2.08)	1 (0.48 to 4)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration at the end of a dosing interval (Ctrough) of tacrolimus

End point title	Plasma concentration at the end of a dosing interval (Ctrough) of tacrolimus[4]

End point description:

The study analysis population for this endpoint consisted of the PKAS. All analyses were performed by type of organ transplant (liver, kidney and heart transplant) and overall. In the case of a combined liver and kidney transplant the participant was counted in the liver transplant group only.

End point type	Primary

End point timeframe:

Day 1 post transplant (blood samples were collected before dosing at (0 hours) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing) and Day 7 (before dosing (0h) and at 0.5h, 1h, 2h, 4h, 8h and 12h after dosing.) (+/- 7 days).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not applicable, only descriptive statistics available for this primary endpoint.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	Overall Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	14	12	38
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	12.6 (± 13.4)	13.41 (± 7.11)	3.54 (± 1.45)	10.04 (± 9.59)
Day 7	7.57 (± 1.8)	9.71 (± 4.03)	8.92 (± 3.59)	8.78 (± 3.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with rejection episodes

End point title	Number of participants with rejection episodes

End point description:

Analysis population consisted of the SAF. A BPAR episode was defined as any acute rejection episode confirmed by biopsy. SRAR: rejection episode that was not treated with new/increased corticosteroid medication, antibodies/any other medication and resolved, irrespective of dose changes. CSAR: rejection episode treated with new/increased corticosteroid medication only and resolved, irrespective of dose changes. CRAR: rejection episode that did not resolve following treatment with corticosteroids (included rejection episodes not treated with corticosteroids first, only with antibodies). AR and BPAR episodes that resolved with further treatment, were unresolved with further treatment and were unresolved with no further treatment were classified under CRARs. Other: rejection episode that cannot be classified into any of the above.

End point type	Secondary

End point timeframe:

Baseline (Visit 1 (within 24 hours prior to treatment)) and up to Day 14 post treatment.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	15	
Units: Participants with rejection episodes				
All Rejections	2	3	0	
Biopsy-proven acute rejections (BPARs)	1	3	0	
Non-Biopsy-proven acute rejections (nonBPARs)	1	0	0	
Any Acute Rejections (ARs)	2	3	0	
Spontaneously resolving Acute Rejections (SRAR)	1	1	0	
Corticosteroid Sensitive Acute Rejections (CSAR)	1	2	0	
Corticosteroid Resistant Acute Rejections (CRAR)	0	0	0	
Any AR - Resolved with further treatment	0	0	0	
Any AR - Unresolved with further treatment	0	0	0	
Any AR - Unresolved with no further treatment	0	0	0	
BPAR - Spontaneously resolving Acute Rejections	1	1	0	
BPAR - Corticosteroid Sensitive Acute Rejections	0	2	0	
BPAR - Corticosteroid Resistant Acute Rejections	0	0	0	
BPAR - Resolved with further treatment	0	0	0	
BPAR - Unresolved with further treatment	0	0	0	
BPAR - Unresolved with no further treatment	0	0	0	
Other acute rejections	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of BPAR

End point title	Severity of BPAR

End point description:

Analysis population consisted of the safety analysis set (SAF). The histological evaluation of the biopsy (to grade BPARs) was performed by the local histopathologist following the Histological Grading of Liver Biopsies for Rejection, the Banff 97 diagnostic categories for renal allograft biopsies – Banff '07 update or the standardised nomenclature of the International Society of Heart and Lung Transplantation (ISHLT). The Rejection Activity Index (RAI) Represents the Sum of Grades (0-3) for portal Inflammation, bile duct inflammation and venular inflammation as collected in the eCRF. The Liver RAI ranges from 0-9. "9999" will be used in place of "N/A" when a category is not applicable to a specific arm/population due to the EudraCT system limitation of only allowing for numerical values.

End point type	Secondary

End point timeframe:

Baseline (Visit 1 (within 24 hours prior to treatment)) and up to Day 14 post treatment.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	15	
Units: Participants with rejection episodes				
Heart - Mild (Grade 1 Rejection (R))	1	9999	9999	
Heart - Moderate (Grade 2 R)	0	9999	9999	
Heart - Severe (Grade 3 R)	0	9999	9999	
Liver RAI score - 0-2 (No Rejection)	9999	0	9999	
Liver RAI score - 3 (Borderline Rejection)	9999	0	9999	
Liver RAI score - 4-5 (Mild Rejection)	9999	1	9999	
Liver RAI score - 6-7 (Moderate Rejection)	9999	2	9999	
Liver RAI score - 8-9 (Severe Rejection)	9999	0	9999	
Kidney - C4d deposition	9999	9999	0	
Kidney - antibody-mediated rejection I	9999	9999	0	
Kidney - antibody-mediated rejection II	9999	9999	0	
Kidney - antibody-mediated rejection III	9999	9999	0	
Kidney - T cell mediated rejection IA	9999	9999	0	
Kidney - T cell mediated rejection IB	9999	9999	0	
Kidney - T cell mediated rejection IIA	9999	9999	0	
Kidney - T cell mediated rejection IIB	9999	9999	0	
Kidney - T cell mediated rejection III	9999	9999	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival

End point title	Patient survival

End point description:

The study analysis population for this endpoint consisted of the SAF. Patient survival was defined as any participant known to be alive at Study Week 2.

End point type	Secondary

End point timeframe:

Baseline (Visit 1 (within 24 hours prior to treatment)) and up to Day 14 post treatment.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	15	
Units: Participants				
Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival

End point title	Graft survival

End point description:

The study analysis population for this endpoint consisted of the SAF. Graft survival was defined as any participant who did not experience graft failure during the study. Graft failure was defined as re-transplantation, nephrectomy, requiring ongoing dialysis, or death. The date of graft failure was the earliest date of any of these events. Kidney transplanted participants who underwent a nephrectomy or who required ongoing dialysis were counted as participants with graft failure with the date of nephrectomy or the date of started dialysis as date of event.

End point type	Secondary

End point timeframe:

Baseline (Visit 1 (within 24 hours prior to treatment)) and up to Day 14 post treatment.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	15	
Units: Participants				
Graft loss	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)

End point description:

The study analysis population for this endpoint consisted of the SAF. An AE was defined as any untoward medical occurrence in a subject administered a study drug and which did not necessarily have a causal relationship with treatment. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. A treatment emergent adverse event (TEAE) was defined as an AE observed after investigational drug administration.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after the final intake of study medication.

End point values	Heart Transplant	Liver Transplant	Kidney Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	15	
Units: Participants				
Any TEAE	14	20	12	
Drug-related TEAEs	10	18	6	
Deaths	0	0	0	
Serious TEAEs	4	9	4	
Drug-related Serious TEAEs	1	5	2	
Deaths Resulting from AEs	0	0	0	
TEAEs Leading to Discontinuation of Study Drug	0	1	0	
Drug-related TEAEs Leading to Disc. of Study Drug	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the final intake of study medication.

Adverse event reporting additional description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose: results in death, is life threatening, results in persistent or significant disability/incapacity, Results in congenital anomaly, or birth defect, requires inpatient hospitalisation or leads to prolongation of hospitalisation, or other medically important events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Heart Transplant

Reporting group description:

This arm consisted of heart transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Reporting group title	Liver Transplant

Reporting group description:

This arm consisted of liver transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Reporting group title	Kidney Transplant

Reporting group description:

This arm consisted of kidney transplant recipients that received Modigraf® (tacrolimus granules) based immunosuppressive treatment regimen post-operatively. Participants received daily dose of oral Modigraf® 0.3 mg/kg/day (given in two doses, 0.15 mg/kg twice daily).

Serious adverse events	Heart Transplant	Liver Transplant	Kidney Transplant
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	9 / 20 (45.00%)	4 / 15 (26.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	3 / 15 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural bile leak			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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
Toxicity to various agents			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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
Mechanical ileus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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
Hepatobiliary disorders			
Hepatic artery occlusion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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
Hepatic artery thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (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

Respiratory, thoracic and mediastinal disorders			
Diaphragmatic paralysis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Heart Transplant	Liver Transplant	Kidney Transplant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 17 (82.35%)	20 / 20 (100.00%)	12 / 15 (80.00%)
Vascular disorders			

Flushing			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 17 (11.76%)	9 / 20 (45.00%)	2 / 15 (13.33%)
occurrences (all)	2	10	2
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Peripheral coldness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Device occlusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Drug withdrawal syndrome			
subjects affected / exposed	0 / 17 (0.00%)	4 / 20 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Face oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Oedema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pyrexia			

subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	3 / 15 (20.00%)
occurrences (all)	0	3	4
Reproductive system and breast disorders			
Penile discharge			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Penile erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Penile pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Scrotal oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Bronchospasm			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Diaphragmatic paralysis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hypopnoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	1	3	0
Respiratory distress			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Delirium tremens			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Withdrawal syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Antithrombin III decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Blood pressure increased			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Drug level below therapeutic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Platelet count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Prothrombin time shortened			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Urine output decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Complications of transplanted liver			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Overdose			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Post procedural bile leak			

subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Procedural hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Procedural site reaction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Scrotal haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Toxicity to various agents			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Transplant failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wound dehiscence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Convulsion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lethargy			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 20 (10.00%)	2 / 15 (13.33%)
occurrences (all)	2	2	3
Coombs positive haemolytic anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Splenic infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	3
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	0 / 17 (0.00%)	4 / 20 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Constipation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	2 / 20 (10.00%)	5 / 15 (33.33%)
occurrences (all)	2	2	5
Gastric haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Haematemesis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Intestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	3 / 20 (15.00%)	5 / 15 (33.33%)
occurrences (all)	0	3	6
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hepatic artery stenosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Portal vein stenosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Nephropathy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Oliguria			

subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Renal failure acute			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	1 / 17 (5.88%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Renal injury			
subjects affected / exposed	2 / 17 (11.76%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Bacterial infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Epstein-Barr virus infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Escherichia urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Fungaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infectious peritonitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Lung infection pseudomonal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin bacterial infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wound infection pseudomonas			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	4 / 20 (20.00%)	0 / 15 (0.00%)
occurrences (all)	1	4	0
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	3 / 17 (17.65%)	2 / 20 (10.00%)	1 / 15 (6.67%)
occurrences (all)	3	2	1
Hypomagnesaemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 20 (5.00%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Hyponatraemia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 20 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Hypophagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Metabolic acidosis			
subjects affected / exposed	0 / 17 (0.00%)	6 / 20 (30.00%)	0 / 15 (0.00%)
occurrences (all)	0	6	0
Metabolic alkalosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2011	The substantial Amendment 1.0 was issued to update contact details of the qualified person for pharmacovigilance and to update the list of excluded concomitant medication by allowing amlodipine as concomitant medication. In addition, it was specified that excluded concomitant medication was prohibited throughout the 2-week study and 7 days prior to the first dose of Modigraf and not prior to study. This substantial amendment had no consequences for the evaluation of data, for patients already included in the study and for the patient information and informed consent (IC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported