Clinical trial results:
Open-label, multicentre, randomized clinical trial to compare the pharmacokinetics of Envarsus® tablets and Advagraf® capsules administered once daily In adult de-novo kidney transplant patients

Summary

EudraCT number	2014-005572-28
Trial protocol	FR
Global end of trial date	24 June 2016

Results information

Result version number	v1 (current)
This version publication date	23 July 2017
First version publication date	23 July 2017

Trial information

Trial identification

Sponsor protocol code	CCD-06235AA1-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.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	Final
Date of interim/final analysis	29 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare pharmacokinetics of tacrolimus early after transplantation following administration of Envarsus® tablets or Advagraf® capsules in adult de-novo kidney transplant recipients.

Protection of trial subjects:

The study was conducted according to the clinical study protocol, the current International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, any local guidelines, and the Declaration of Helsinki (1964 and amendments).

At all visits, from screening onwards, concomitant medication, AEs, and vital signs were recorded.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 76 patients were enrolled according to inclusion and exclusion criteria; of these, 75 patients were randomized to treatment.

Pre-assignment

Screening details:

Screening was performed from 0 to 14 days prior to kidney transplantation. At the screening visit, inclusion/exclusion criteria were assessed.

Day 0, the day of transplantation, was defined as the day on which the transplanted organ was reperfused in vivo with the recipient's blood.

Period 1

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

Blinding implementation details:

Open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Envarsus

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tacrolimus (Envarsus)
Investigational medicinal product code	
Other name	Envarsus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Envarsus (tacrolimus) prolonged-release tablets: 0.75 mg, 1.0 mg, and 4.0 mg dose strengths.

Envarsus tablets (oral administration] once daily in the morning starting at the dose of 0.17 mg/kg). The dose of Envarsus was maintained constant until Day 3 and adjusted on Days 4, 8, 15, and 22 according to the trough levels, assessed at the local laboratory the day prior to the dose change.

The dose of Envarsus was adjusted on the scheduled days to maintain whole blood tacrolimus trough levels within the target range. Target trough level range was within 5-15 ng/mL (average 10 ng/mL) from Day 2 to Day 15 and within 5-10 ng/mL (average 7.5 ng/mL) from Day 16 to Day 28.

Day 0, the day of transplantation, was defined as the day on which the transplanted organ was reperfused in vivo with the recipient's blood. Treatment with the study drug was initiated within 24 hours of transplantation (graft reperfusion) and continued for 28 consecutive days.

Arm title	Advagraf

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Tacrolimus (Advagraf)
Investigational medicinal product code	
Other name	Advagraf
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Advagraf (tacrolimus) prolonged-release hard capsules provided in 0.5 mg, 1.0 mg, 3.0 mg, and 5.0 mg dose strengths.
Advagraf capsules (oral administratioin) once daily in the morning starting at the dose of 0.2 mg/kg.

The dose of Advagraf was maintained constant until Day 3 and adjusted at Days 4, 8, 15, and 22 according to the trough levels, assessed at the local laboratory the day prior the dose change.

The doses of Advagraf were adjusted on the scheduled days to maintain whole blood tacrolimus trough levels within the target range. Target trough level range was within 5-15 ng/mL (average 10 ng/mL) from Day 2 to Day 15 and within 5-10 ng/mL (average 7.5 ng/mL) from Day 16 to Day 28.

Day 0, the day of transplantation, was defined as the day on which the transplanted organ was reperfused in vivo with the recipient's blood. Treatment with the study drug was initiated within 24 hours of transplantation (graft reperfusion) and continued for 28 consecutive days.

Number of subjects in period 1	Envarsus	Advagraf
Started	37	38
Completed	31	32
Not completed	6	6
Consent withdrawn by subject	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Envarsus
Reporting group description: -	
Reporting group title	Advagraf
Reporting group description: -	

Reporting group values	Envarsus	Advagraf	Total
Number of subjects	37	38	75
Age categorical Units: Subjects			
Adults (18-64 years)	21	29	50
From 65-84 years	16	9	25
Age continuous Units: years			
arithmetic mean	59.9	53.4	
standard deviation	± 14	± 15.9	-
Gender categorical Units: Subjects			
Female	12	8	20
Male	25	30	55
Race Units: Subjects			
White	37	38	75

End points

End points reporting groups

Reporting group title	Envarsus
Reporting group description: -	
Reporting group title	Advagraf
Reporting group description: -	

Primary: 1_Tacrolimus daily dose normalized area under the whole blood drug concentration-time curve; AUC 0-24h/Dose

End point title	1_Tacrolimus daily dose normalized area under the whole blood drug concentration-time curve; AUC 0-24h/Dose

End point description:

Tacrolimus AUC0-24h normalized to the daily dose (AUC0-24h/Dose) was evaluated on Day 1, Day 3, Day 7 and Day 14.
The AUC0-24h (AUC0-24h/Dose can be considered an index of oral bioavailability.

The following blood samples for the 0-24 hour PK profiles were drawn: 0.00 (pre-dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00, and 24.00 hours after the morning dose (a total of 13 samples).

Pharmacokinetic (PK) variables were calculated based on individual blood concentration-time data using non-compartmental methods.

Note:
1) The actual number of patients (N) contributing to the data on each evaluation day is shown under the results table.
2) For the geometric coefficient of variation, the sign ± was assigned automatically by the database system.
3) Data were summarized using descriptive statistics by treatment and visit.

End point type	Primary

End point timeframe:

From time 0 (pre-dose) to 24 hours post dose on Day 1, Day 3, Day 7 and Day 14.

End point values	Envarsus	Advagraf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[1]	35[2]		
Units: ng.h/mL/mg dose				
geometric mean (geometric coefficient of variation)				
Day 1	19.02 (± 43.5)	20.09 (± 41)		
Day 3	45.63 (± 38.4)	34.6 (± 39.9)		
Day 7	45.21 (± 42.3)	36.25 (± 44.4)		
Day 14	50.4 (± 41.3)	35.35 (± 44.2)		

Notes:

[1] - PK population
Day 1 N=31
Day 3 N=33
Day 7 N=28
Day 14 N=28

[2] - PK population
Day 1 N=33
Day 3 N=33
Day 7 N=31
Day 14 N=30

Statistical analyses

Statistical analysis title	AUC0-24h (AUC0-24h/Dose); Day 3

Statistical analysis description:

Day 3
Envarsus vs Advagraf
Normalised AUC0-24h: Normalised AUC0-24h = AUC0-24h / dose on that day.

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=66 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Envarsus v Advagraf
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.007 [4]
Method	ANOVA
Parameter estimate	LSMean adjusted
Point estimate	131.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	111.82
upper limit	155.56

Notes:

[3] - Descriptive characterisation of the PK parameters for the study drugs was performed.
No formal hypothesis was predefined.
[4] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Statistical analysis title	AUC0-24h (AUC0-24h/Dose); Day 7

Statistical analysis description:

Day 7
Envarsus vs Advagraf
Normalised AUC0-24h: Normalised AUC0-24h = AUC0-24h / dose on that day.

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=59 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Advagraf v Envarsus
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.051 [6]
Method	ANOVA
Parameter estimate	LSMean adjusted
Point estimate	124.73

Confidence interval	
level	90 %
sides	2-sided
lower limit	103.67
upper limit	150.06

Notes:

[5] - Descriptive characterisation of the PK parameters for the study drugs was performed.
No formal hypothesis was predefined.
[6] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Statistical analysis title	AUC0-24h (AUC0-24h/Dose); Day 14

Statistical analysis description:

Day 14
Envarsus vs Advagraf
Normalised AUC0-24h: Normalised AUC0-24h = AUC0-24h / dose on that day.

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=58 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Envarsus v Advagraf
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.002 [8]
Method	ANOVA
Parameter estimate	LSMean adjusted
Point estimate	142.57
Confidence interval	
level	90 %
sides	2-sided
lower limit	118.63
upper limit	171.35

Notes:

[7] - Descriptive characterisation of the PK parameters for the study drugs was performed.
No formal hypothesis was predefined.
[8] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Primary: 2_Percent fluctuation [(Cmax-Cmin)*100/Cavg]

End point title	2_Percent fluctuation [(Cmax-Cmin)*100/Cavg]

End point description:

Tacrolimus maximum whole blood drug concentration (Cmax), average whole blood drug concentration (Cavg), minimum whole blood drug concentration (Cmin), % fluctuation [(Cmax-Cmin)*100/Cavg], following the morning dose of Day 1, Day 3, Day 7, and Day 14.

Note:
1) The actual number of patients (N) contributing to the data on each evaluation day is shown under the results table.
2) For the geometric coefficient of variation, the sign ± was assigned automatically by the database system.

End point type	Primary

End point timeframe:

From time 0 (pre-dose) to 24 hours post dose (AUC 0-24h) on Day 1, Day 3, Day 7 and Day 14.

End point values	Envarsus	Advagraf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[9]	35[10]		
Units: percent				
geometric mean (geometric coefficient of variation)				
Day 1	180.74 (± 30.4)	148.52 (± 25.6)		
Day 3	82.97 (± 43)	118.24 (± 30.2)		
Day 7	94.24 (± 46.1)	137.9 (± 29.1)		
Day 14	98.57 (± 43.8)	135.78 (± 35.2)		

Notes:

[9] - Pharmacokinetic population
Day 1 N=31
Day 3 N=33
Day 7 N=28
Day 14 N=28
[10] - Pharmacokinetic population
Day 1 N=33
Day 3 N=33
Day 7 N=31
Day 14 N=30

Statistical analyses

Statistical analysis title	Treatment effect ratio Envarsus/Advagraf; Day 3

Statistical analysis description:

% Fluctuation normalized to the daily dose [AUC0-24h/Dose] on Day 3, Day 7 and Day 14 were log-transformed to the natural logarithmic scale and then analyzed (analysis of variance (ANOVA) model with treatment as a fixed effect).

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=66 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Envarsus v Advagraf
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.001 [12]
Method	ANOVA
Parameter estimate	Treatment effect ratio
Point estimate	70.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	60.09
upper limit	81.95

Notes:

[11] - Descriptive characterisation of the PK parameters for the study drugs was performed.
No formal hypothesis was predefined.

[12] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Statistical analysis title	Treatment effect ratio Envarsus/Advagraf; Day 7

Statistical analysis description:

% Fluctuation normalized to the daily dose [AUC0-24h/Dose] on Day 3, Day 7 and Day 14 were log-transformed to the natural logarithmic scale and then analyzed (analysis of variance (ANOVA) model with treatment as a fixed effect).

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=59 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Envarsus v Advagraf
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.001 [14]
Method	ANOVA
Parameter estimate	Treatment effect ratio
Point estimate	68.34
Confidence interval	
level	90 %
sides	2-sided
lower limit	58.21
upper limit	80.23

Notes:

[13] - Descriptive characterisation of the PK parameters for the study drugs was performed.
No formal hypothesis was predefined.
[14] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Statistical analysis title	Treatment effect ratio Envarsus/Advagraf; Day 14

Statistical analysis description:

% Fluctuation normalized to the daily dose [AUC0-24h/Dose] on Day 3, Day 7 and Day 14 were log-transformed to the natural logarithmic scale and then analyzed (analysis of variance (ANOVA) model with treatment as a fixed effect).

The ratios of adjusted geometric means between the 2 groups were calculated with 90% (2-sided confidence intervals).

N=58 patients were included in this analysis.
The value N=68, shown below is due to innate error of the EudraCT database.

Comparison groups	Envarsus v Advagraf
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.004 [16]
Method	ANOVA
Parameter estimate	Treatment effect ratio
Point estimate	72.6

Confidence interval	
level	90 %
sides	2-sided
lower limit	60.87
upper limit	86.59

Notes:

[15] - Descriptive characterisation of the PK parameters for the study drugs was performed. No formal hypothesis was predefined.

[16] - ANOVA Analysis using logged values. LSMean adjusted for treatment, back-transformed to original scale.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time of patient informed consent signature to study completion (Day 28) or discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Envarsus
Reporting group description: -	
Reporting group title	Advagraf

Reporting group description: -

Serious adverse events	Envarsus	Advagraf	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 33 (45.45%)	11 / 36 (30.56%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
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			
Pyrexia			

subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 33 (3.03%)	3 / 36 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	3 / 33 (9.09%)	4 / 36 (11.11%)	
occurrences causally related to treatment / all	3 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			

subjects affected / exposed	1 / 33 (3.03%)	3 / 36 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hemorrhagic disorder			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial prostatitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Septic shock			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Envarsus	Advagraf	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	36 / 36 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	5	
Haematoma			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Hot flush			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Lymphocele			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
General disorders and administration			

site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 33 (21.21%)	9 / 36 (25.00%)	
occurrences (all)	8	9	
Asthenia			
subjects affected / exposed	2 / 33 (6.06%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Pain			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Catheter site pain			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Chest pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 33 (18.18%)	6 / 36 (16.67%)	
occurrences (all)	9	7	
Anxiety			
subjects affected / exposed	2 / 33 (6.06%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Confusional state			
subjects affected / exposed	2 / 33 (6.06%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Injury, poisoning and procedural complications			
Procedural pain			

subjects affected / exposed	7 / 33 (21.21%)	8 / 36 (22.22%)	
occurrences (all)	7	8	
Complications of transplanted kidney			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Overdose			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 33 (15.15%)	7 / 36 (19.44%)	
occurrences (all)	5	9	
Tremor			
subjects affected / exposed	4 / 33 (12.12%)	4 / 36 (11.11%)	
occurrences (all)	4	4	
Neuralgia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 33 (57.58%)	20 / 36 (55.56%)	
occurrences (all)	19	20	
Lymphopenia			
subjects affected / exposed	5 / 33 (15.15%)	5 / 36 (13.89%)	
occurrences (all)	6	7	
Leukocytosis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 36 (16.67%)	
occurrences (all)	0	6	
Iron deficiency anaemia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Thrombocytopenia			

subjects affected / exposed	3 / 33 (9.09%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 33 (30.30%)	9 / 36 (25.00%)	
occurrences (all)	10	11	
Abdominal pain			
subjects affected / exposed	7 / 33 (21.21%)	8 / 36 (22.22%)	
occurrences (all)	9	8	
Diarrhoea			
subjects affected / exposed	8 / 33 (24.24%)	7 / 36 (19.44%)	
occurrences (all)	9	7	
Nausea			
subjects affected / exposed	5 / 33 (15.15%)	2 / 36 (5.56%)	
occurrences (all)	7	2	
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	6	
Haemorrhoids			
subjects affected / exposed	1 / 33 (3.03%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Scar pain			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	10 / 33 (30.30%)	14 / 36 (38.89%)	
occurrences (all)	10	15	
Proteinuria			
subjects affected / exposed	3 / 33 (9.09%)	4 / 36 (11.11%)	
occurrences (all)	3	4	
Renal impairment			

subjects affected / exposed	2 / 33 (6.06%)	4 / 36 (11.11%)	
occurrences (all)	2	4	
Bladder spasm			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Dysuria			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Hypertonic bladder			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Pain in extremity			
subjects affected / exposed	3 / 33 (9.09%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	3 / 33 (9.09%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 33 (18.18%)	4 / 36 (11.11%)	
occurrences (all)	6	4	
Bacterial prostatitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	5 / 33 (15.15%)	6 / 36 (16.67%)	
occurrences (all)	5	6	
Diabetes mellitus			

subjects affected / exposed	3 / 33 (9.09%)	6 / 36 (16.67%)	
occurrences (all)	3	6	
Hyperglycemia			
subjects affected / exposed	2 / 33 (6.06%)	4 / 36 (11.11%)	
occurrences (all)	3	4	
Vitamin D deficiency			
subjects affected / exposed	2 / 33 (6.06%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Hypocalcaemia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	4	
Acidosis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Fluid retention			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Hypercalcaemia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	3 / 33 (9.09%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Hyperkalaemia			
subjects affected / exposed	4 / 33 (12.12%)	6 / 36 (16.67%)	
occurrences (all)	4	9	
Hyperphosphataemia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Hypoalbuminaemia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	5 / 33 (15.15%)	9 / 36 (25.00%)	
occurrences (all)	5	9	
Hypophosphataemia			

subjects affected / exposed	5 / 33 (15.15%)	4 / 36 (11.11%)	
occurrences (all)	5	4	
Hypovitaminosis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2015	The dose of the study drug was to be adjusted on the scheduled days to maintain whole blood tacrolimus trough levels within the target range. Target trough level range were within 5–15 ng/mL (average 10 ng/mL) from Day 2 to Day 14 and within 5-10 ng/mL (average 7.5 ng/mL) from Day 15 to Day 28. Update of the study inclusion criteria; patients with BMI outside the range 15-35 kg/m2 were excluded from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported