Clinical trial results:
A PHASE II, OPEN LABEL, PARALLEL GROUP, MULTI-CENTER STUDY TO COMPARE THE PHARMACOKINETICS OF TACROLIMUS IN ADULT SUBJECTS UNDERGOING PRIMARY ALLOGRAFT TRANSPLANTATION RECEIVING AN ADVAGRAF OR PROGRAF BASED IMMUNOSUPPRESSIVE REGIMEN, INCLUDING A LONG-TERM FOLLOW-UP

Summary

EudraCT number	2010-019859-21
Trial protocol	AT GB IT BE
Global end of trial date	15 November 2013

Results information

Result version number	v1 (current)
This version publication date	23 March 2016
First version publication date	28 May 2015

Trial information

Trial identification

Sponsor protocol code	PMR-EC-1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01332201
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	Final
Date of interim/final analysis	15 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2013
Global end of trial reached?	Yes
Global end of trial date	15 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the systemic exposure (AUC0-24h) of tacrolimus for Advagraf versus Prograf after the first dose and following repeated administration in patients undergoing primary heart, lung, pancreas (including simultaneous pancreas kidney (SPK)) transplantation.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH 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:

The Investigational Medicinal Products (IMP) Advagraf and Prograf were provided by the Sponsor. Antibodies (Anti-thymocyte globulin (ATG) was recommended), Mycophenolate Mofetil (MMF) and corticosteroids were not considered IMP in this study and were not provided by the Sponsor, but were provided by the local hospital pharmacy. Antibody Induction: the first dose of antibody induction therapy was to be given intravenously (IV) within 24 hours after skin closure. The initial dose and any later dose adjustments followed the routine practice of the center. The recommended dosing regimen for MMF was as follows: a loading dose of 1g of MMF given pre-operatively. The first post-operative dose of MMF administered within 72 hours following reperfusion. The daily dose of 2g given orally and split into two doses (equals 1g twice daily) for the first 14 days. Thereafter the daily dose was reduced to 1g given in two doses (equals 0.5g twice daily). From day 42 the dose of MMF was in accordance with the routine practice of the center. Corticosteroids: day -3 (500mg or less i.v. bolus pre, intra or post-operatively), day -2 (125mg i.v. bolus) for heart transplantation recipients. Day -1 (500mg or less i.v. bolus pre, intra or post-operatively), day 1 (125mg i.v. bolus) for lung/pancreas/SPK recipients. Prednisolone or equivalent: day -1 to 14 (20mg/day), day 15 to 28 (15mg/day), day 29 to 42 (10mg/day), Day 43 to 407 (≥ 5mg/day) for heart transplantation recipients. Day 2 to 14 (20mg/day), day 15 to 28 (15mg/day), day 29 to 42 (10mg/day), Day 43 to 407 (≥ 5mg/day) for lung/pancreas/SPK recipients.

Evidence for comparator: -

Actual start date of recruitment	23 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 1

Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Taiwan: 5
Worldwide total number of subjects	17
EEA total number of subjects	12

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)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multinational, multicenter study was conducted at 6 contracted sites in a total of 5 countries: Austria, France Italy (2 sites), Taiwan and United Kingdom. Due to poor recruitment the study was terminated early.

Pre-assignment

Screening details:

Eligibility took place baseline day -3 and day -2 prior to day 1/Visit 1 for heart transplant recipients and on day -1 for lung/pancreas/SPK recipients. Screening assessments: patient data, pregnancy test, donor/organ data, surgical details, physical examination (including body weight), vital signs and routine laboratory evaluations were performed.

Period 1

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

Blinding implementation details:

Not applicable as this is an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Advagraf

Arm description:

Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.

Arm type	Experimental
Investigational medicinal product name	Advagraf
Investigational medicinal product code	FK506E (MR4)
Other name	MR4, Tacrolimus, Tacrolimus modified release, Tacrolimus prolonged release formulation
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Advagraf® was defined as study drug, considered IMP and provided by the Sponsor, available as hard gelatin capsules with 0.5 mg, 1 mg, 3 mg and 5 mg of tacrolimus. Dosing of Advagraf: heart transplant recipients: initial dose was 0.075mg/kg/day given orally (one dose), administered at 3 days (72 hours) post skin closure (Day 1) in the morning. Lung transplant recipients: initial dose was 0.075mg/kg/day given orally in one dose, administered in the morning following skin closure. Pancreas/SPK transplant recipients: initial dose was 0.2 mg/kg/day orally (one dose), administered in the morning following skin closure. Subsequent doses were taken orally once a day only in the morning. Advagraf was taken on an empty stomach or at least one hour before or 2 to 3 hours after meal. Dose adjustments were based on clinical evidence of efficacy/occurrence of adverse events (AEs)/observing the following recommended Tacrolimus blood trough levels: Day 1-42 10-20 ng/ml, Day 43-407 5-15 ng/ml.

Arm title	Prograf

Arm description:

Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.

Arm type	Active comparator
Investigational medicinal product name	Prograf
Investigational medicinal product code	FK506
Other name	Tacrolimus, Tacrolimus immediate release formulation
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Prograf® was defined as study drug, considered to be IMP and provided by the Sponsor, available as hard gelatin capsules with 0.5 mg, 1 mg and 5 mg of tacrolimus. Dosing of Prograf: heart transplant and lung recipients: initial total daily dose was 0.075mg/kg/day given orally (two doses) (equals 0.0375mg/kg) in the morning and the evening, first dose was to be administered 3 days (72 hours) post skin closure in the morning. Pancreas/SPK transplant recipients: initial dose was 0.2mg/kg/day given orally in two doses (equals 0.1mg/kg), first dose was to be administered in the morning following skin closure. Subsequent doses were taken orally twice a day in the morning and evening. Prograf was taken on an empty stomach or at least one hour before or 2 to 3 hours after the meal. Dose adjustments were based on clinical evidence of efficacy/occurrence of AE's/observing the following recommended Tacrolimus blood trough levels: Day 1-42 10-20 ng/ml, Day 43-407 5-15 ng/ml.

Number of subjects in period 1	Advagraf	Prograf
Started	8	9
Completed	6	8
Not completed	2	1
Consent withdrawn by subject	1	-
Randomized but not treated	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Advagraf
Reporting group description:	
Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.	
Reporting group title	Prograf
Reporting group description:	
Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.	

Reporting group values	Advagraf	Prograf	Total
Number of subjects	8	9	17
Age categorical			
Age values provided are for the total randomized population.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	9	17
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Gender values provided are for the Full Analysis Set (FAS) population. The FAS consisted of all patients transplanted and randomized who received at least one dose of study drug.			
Units: Subjects			
Female	4	0	4
Male	3	9	12
Not recorded	1	0	1

End points

End points reporting groups

Reporting group title	Advagraf
Reporting group description:	
Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.	
Reporting group title	Prograf
Reporting group description:	
Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.	

Primary: Systemic exposure area under the plasma concentration – time curve (AUC)0-24h of tacrolimus after first dose and under steady state conditions

End point title	Systemic exposure area under the plasma concentration – time curve (AUC)0-24h of tacrolimus after first dose and under steady state conditions[1]
End point description:	
FAS population. AUC0-24h was calculated using the trapezoidal rule. N equals number of patients with pharmacokinetic data.	
End point type	Primary
End point timeframe:	
Day 1, Day 3, Day 7 and Day 42. For Days 3, 7 and 42 profile was to be performed after a minimum of 3 days without a dose change.	

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: Since the enrollment for the study was terminated early due to poor recruitment, the data obtained are insufficient to make any meaningful comparison of systemic exposure of tacrolimus between the 2 treatment regimens.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: ng/mL.h				
arithmetic mean (standard deviation)				
Day 1 [N=7,8]	244.97 (± 214.59)	339.91 (± 197.89)		
Day 3 [N=7,9]	439.55 (± 287.91)	412.62 (± 233.45)		
Day 7 [N=6,5]	437.34 (± 222.87)	231.47 (± 34.51)		
Day 42 [N=5,6]	335.52 (± 41.7)	334.03 (± 140.87)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety as assessed by recording adverse events, laboratory assessments and vital signs

End point title	Safety as assessed by recording adverse events, laboratory assessments and vital signs[2]

End point description:

Treatment-emergent Adverse Events (TEAEs) were AEs observed at the same time as or after starting administration of the study drug, and before the start of another treatment, if any. A treatment-related TEAE was defined as a TEAE whose relationship to study drug was assessed as "possible" or "probable" by the investigator, or whose relationship to study drug is missing. FAS population. Only one death occurred after patient was discontinued from the study but during serious adverse event 30 day follow-up window.

End point type	Primary

End point timeframe:

From the first dose of study drug until end of study. Treatment was a total of 58 weeks.

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: Since the enrollment for the study was terminated early due to poor recruitment, the data obtained are insufficient to make any meaningful comparison of systemic exposure of tacrolimus between the 2 treatment regimens.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Participants				
Any TEAE	7	9		
Drug-related TEAEs	5	7		
Deaths	0	1		
Serious TEAEs	2	6		
Drug-related Serious TEAEs	1	2		
TEAEs Leading to Discontinuation	0	0		
Drug-related TEAEs Leading to Discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax)

End point title	Maximum Concentration (Cmax)

End point description:

FAS population. N equals number of patients with pharmacokinetic data.

End point type	Secondary

End point timeframe:

Day 1, Day 3, Day 7 and Day 42.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 [N=7,9]	20.03 (± 15.77)	20.45 (± 13.17)		
Day 3 [N=7,9]	29.46 (± 13.35)	24.32 (± 13.67)		
Day 7 [N=6,5]	29.32 (± 15.41)	16.97 (± 6.56)		
Day 42 [N=5,6]	27.16 (± 5.85)	25.08 (± 11.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Attain Maximum Concentration (Tmax)

End point title	Time to Attain Maximum Concentration (Tmax)

End point description:

FAS population. If Cmax occurred on more than one time point, the first time it occurred was considered for tmax. N equals number of patients with pharmacokinetic data.

End point type	Secondary

End point timeframe:

Day 1, Day 3, Day 7 and Day 42.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: hours				
median (full range (min-max))				
Day 1 [N=7,9]	4 (1 to 6)	3 (0.5 to 4)		
Day 3 [N=7,9]	2 (1 to 24)	2 (1 to 4)		
Day 7 [N=6,5]	2.5 (1 to 8)	2 (1 to 3)		
Day 42 [N=5,6]	2 (1 to 4)	2 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration prior to the morning dose C24 (24 hours after morning dose of once daily advagraf or 12 hours after evening dose of twice daily prograf)

End point title	Concentration prior to the morning dose C24 (24 hours after morning dose of once daily advagraf or 12 hours after evening

	dose of twice daily prograf)

End point description:

FAS population. N equals number of patients with pharmacokinetic data.

End point type	Secondary

End point timeframe:

Day 1, Day 3, Day 7 and Day 42.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 [N=7,8]	6.91 (± 5.82)	13.6 (± 7.61)		
Day 3 [N=7,9]	15.83 (± 13.09)	14.72 (± 8.61)		
Day 7 [N=6,5]	13.63 (± 8.38)	7.69 (± 1.64)		
Day 42 [N=5,6]	9.19 (± 1.8)	10.91 (± 4.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rejection Episodes

End point title	Rejection Episodes

End point description:

FAS population.

End point type	Secondary

End point timeframe:

Up to 58 weeks.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Participants				
Biopsy Confirmed Acute Rejection (BCAR)	0	2		
Clinical Signs of Acute Rejection	1	0		
Clinical Diagnosis of Acute Rejection	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject survival

End point title	Subject survival

End point description:

FAS population. Only one death occurred in the study.

End point type	Secondary

End point timeframe:

Up to 58 weeks.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Participants	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival

End point title	Graft survival

End point description:

FAS population. Graft loss was defined as retransplantation, nephrectomy, death or dialysis ongoing at the End of Study or at discontinuation unless superseded by follow-up information.

End point type	Secondary

End point timeframe:

Up to 58 weeks.

End point values	Advagraf	Prograf		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: Participants	7	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until end of study. TEAEs were AEs observed at the same time as or after starting study drug, and before the start of another treatment, if any. Treatment was a total of 58 weeks.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. FAS population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Advagraf

Reporting group description:

Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.

Reporting group title	Prograf

Reporting group description:

Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.

Serious adverse events	Advagraf	Prograf	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	6 / 9 (66.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epstein-Barr virus associated lymphoproliferative disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
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			
Surgical procedure repeated			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (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			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreas transplant rejection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
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 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BK virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Candida sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Advagraf	Prograf	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid neoplasm			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Circulatory collapse			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Prostatism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Respiratory, thoracic and mediastinal disorders			
Bronchostenosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 7 (28.57%)	3 / 9 (33.33%)	
occurrences (all)	3	3	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Organising pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pulmonary hilum mass			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Drug level increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Electroencephalogram abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Plasma cells increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tumour marker increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Incisional hernia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Wound dehiscence			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Loss of consciousness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 7 (42.86%)	4 / 9 (44.44%)	
occurrences (all)	5	4	
Iron deficiency anaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	
occurrences (all)	3	3	
Lymphadenopathy			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Thrombocythaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	3 / 9 (33.33%)	
occurrences (all)	4	3	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 9 (33.33%)	
occurrences (all)	3	5	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	3	
Inguinal hernia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Melaena			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	0 / 7 (0.00%)	3 / 9 (33.33%)	
occurrences (all)	0	3	
Stomach discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hepatic cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hepatic function abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hepatic lesion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypertransaminasaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Keratosis pilaris			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nocturia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal failure chronic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Ureteric stenosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Osteolysis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Infections and infestations			
BK virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Vulvovaginal candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hyperlipidaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 9 (22.22%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hypophosphataemia			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 9 (11.11%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to poor recruitment. The data obtained are insufficient to draw firm conclusions from the results of this study.

Notes: