Clinical trial results:
Multi-center, open-label, prospective, randomized, parallel group study investigating a tacrolimus Hexal® based regimen versus a Prograf® based regimen in de novo renal transplant recipients

Summary

EudraCT number	2011-003795-36
Trial protocol	DE
Global end of trial date	20 August 2015

Results information

Result version number	v1 (current)
This version publication date	04 September 2016
First version publication date	04 September 2016

Trial information

Trial identification

Sponsor protocol code	CERL080ADE27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01649427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	20 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

PHASE I: The primary objective of Phase I of the study was to demonstrate that the pharmacokinetics of Tacrolimus Hexal® assessed by the ratio of the AUC0-12h over a 1-month period post-transplantation is comparable to Prograf® in renal transplant patients. PHASE II (included patients enrolled in Phase I): The primary objective of Phase II study was to demonstrate non-inferiority in renal function assessed by glomerular filtration rate (GFR) (Nankivell formula) between both treatment arms at Month 6 post-transplantation in renal transplant patients. The Phase II of the study was not conducted; therefore endpoints of Phase II were additionally evaluated for the patients of Phase I.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2012
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	Germany: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	73
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

81 patients were randomized, but only 73 patients were assigned drug.

Pre-assignment

Screening details:

This is a 2-phase study:
PHASE I:
In 1st phase of study, PK parameters were evaluated in total of 60 evaluable patients (30 patients per treatment group)
PHASE II:
Phase II was not conducted.

Period 1

Period 1 title	Completion of treatment (Phase I) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus Hexal®

Arm description:

Investigational therapy: one capsule containing 0.5mg, 1mg or 5mg Tacrolimus Hexal®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

nvestigational therapy: one capsule containing 0.5mg, 1mg or 5mg Tacrolimus Hexal®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Arm title	Prograf®

Arm description:

Control therapy: one capsule containing 0.5 mg, 1mg or 5mg Prograf®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Arm type	Active comparator
Investigational medicinal product name	Prograf
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Control therapy: one capsule containing 0.5 mg, 1mg or 5mg Prograf®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Number of subjects in period 1	Tacrolimus Hexal®	Prograf®
Started	35	38
Completed	24	26
Not completed	11	12
Consent withdrawn by subject	8	7
Graft loss	-	1
Adverse event, non-fatal	1	1
Surgical problems during nephrectomy	2	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus Hexal®
Reporting group description:	
Investigational therapy: one capsule containing 0.5mg, 1mg or 5mg Tacrolimus Hexal®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®	
Reporting group title	Prograf®
Reporting group description:	
Control therapy: one capsule containing 0.5 mg, 1mg or 5mg Prograf®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®	

Reporting group values	Tacrolimus Hexal®	Prograf®	Total
Number of subjects	35	38	73
Age categorical			
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)	35	38	73
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	47.9	47.2	
standard deviation	± 9.9	± 11.8	-
Gender, Male/Female			
Units: Subjects			
Female	6	9	15
Male	29	29	58

End points

End points reporting groups

Reporting group title	Tacrolimus Hexal®
Reporting group description:	
Investigational therapy: one capsule containing 0.5mg, 1mg or 5mg Tacrolimus Hexal®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®	
Reporting group title	Prograf®
Reporting group description:	
Control therapy: one capsule containing 0.5 mg, 1mg or 5mg Prograf®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®	

Primary: ANCOVA model for change in Nankivell GFR (mL/min) at Month 6, without replacement of missing values (Full Analysis set)

End point title	ANCOVA model for change in Nankivell GFR (mL/min) at Month 6, without replacement of missing values (Full Analysis set)
End point description:	
Change in Nankivell glomerular filtration rate (GFR) from baseline to 6 months Glomerular Filtration Rate (GFR): The GFR is the best clinical estimate of renal function in health and disease, and correlates well with the clinical severity of renal function disturbances. Several studies have shown that in patients with progressive renal disease, GFR declines or reciprocal serum creatinine levels elevate linearly over time in a predictable manner. With the help of the serum creatinine values, the GFR was calculated via Nankivell formula.	
End point type	Primary
End point timeframe:	
month 6	

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	27		
Units: mL/min				
least squares mean (confidence interval 95%)	47.65 (41.7 to 53.6)	38.6 (31.32 to 45.89)		

Statistical analyses

Statistical analysis title	Change in GFR
Comparison groups	Tacrolimus Hexal® v Prograf®
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	ANCOVA

Primary: ANOVA for dose-normalized Tacrolimus 12-h-AUC (h/103*L) at Month 1

End point title	ANOVA for dose-normalized Tacrolimus 12-h-AUC (h/103*L) at Month 1[1]

End point description:

Compares the PK of Tacrolimus Hexal® assessed by the ratio of the AUC0-12h over one month period post transplantation vs. Prograf® in renal transplant patients

End point type	Primary

End point timeframe:

end of month 1

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: Only summary statistics provided.

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: h/103*L				
least squares mean (confidence interval 90%)				
Adjusted, log-transformed Estimates (ANOVA)	2.944 (2.783 to 3.105)	3.02 (2.811 to 3.228)		
Adjusted, back-transformed Estimates (ANOVA)	18.991 (16.163 to 22.314)	20.484 (16.63 to 25.231)		

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of biopsy-proven acute rejection (BPAR), graft loss and death until Month 6 and Month 12 (Full Analysis Set)

End point title	The incidence of biopsy-proven acute rejection (BPAR), graft loss and death until Month 6 and Month 12 (Full Analysis Set)

End point description:

The key secondary objective was to assess the incidence of individual endpoints BPAR, graft loss and death at Month 6 post-transplantation. The secondary objective for Phase I was to assess the incidence of treatment failure (defined as BPAR, graft loss or death) between the 2 arms at Month 1 post-transplantation. Phase II of the study was not conducted and so this analysis was not performed.

End point type	Secondary

End point timeframe:

baseline, month 6 and month 12

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	38		
Units: mL/min				
number (confidence interval 95%)				
Biopsy proven acute rejection (BPAR)	2 (0.7 to 19.16)	3 (1.66 to 21.38)		
Graft loss	0 (0 to 10)	1 (0.07 to 13.81)		
Death	0 (0 to 10)	1 (0.07 to 13.81)		
Composite: BPAR, graft loss or death	2 (0.7 to 19.16)	4 (2.94 to 24.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: ANCOVA model for change in CKD-EPI GFR at Month 6 post-transplantation

End point title	ANCOVA model for change in CKD-EPI GFR at Month 6 post-transplantation

End point description:

ANCOVA model for change in CKD-EPI Glomerular Filtration Rate (GFR)[ml/min] without replacement of missing values

End point type	Secondary

End point timeframe:

at Month 6

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	27		
Units: mL/min				
least squares mean (standard error)	48.33 (± 3.84)	39.77 (± 4.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: ANCOVA model for change in MDRD GFR (ml/min) at month 6, without replacement of missing values

End point title	ANCOVA model for change in MDRD GFR (ml/min) at month 6, without replacement of missing values

End point description:

MDRD GFR

End point type	Secondary
End point timeframe: month 6	

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	38		
Units: (ml/min)				
least squares mean (confidence interval 95%)	46.2 (37.62 to 54.79)	38.52 (28.64 to 48.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: ANCOVA model for change in Cockcroft-Gault GFR (ml/min) at month 6, without replacement of missing values

End point title	ANCOVA model for change in Cockcroft-Gault GFR (ml/min) at month 6, without replacement of missing values
End point description: change in Cockcroft-Gault GFR	
End point type	Secondary
End point timeframe: month 6	

End point values	Tacrolimus Hexal®	Prograf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	38		
Units: (ml/min)				
least squares mean (confidence interval 95%)	60.45 (52.48 to 68.41)	46.45 (36.89 to 56.02)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Tacrolimus Hexal®

Reporting group description:

Investigational therapy: one capsule containing 0.5mg, 1mg or 5mg Tacrolimus Hexal®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Reporting group title	Prograf®

Reporting group description:

Control therapy: one capsule containing 0.5 mg, 1mg or 5mg Prograf®, one tablet containing 180mg or 360mg Myfortic®, corticosteroids and one vial containing 20mg lyophilisate Simulect®

Serious adverse events	Tacrolimus Hexal®	Prograf®	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 35 (54.29%)	17 / 39 (43.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PROSTATE CANCER			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
VARICOSE VEIN			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
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			

IMPAIRED HEALING			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPLANT SITE EXTRAVASATION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
KIDNEY TRANSPLANT REJECTION			
subjects affected / exposed	2 / 35 (5.71%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP APNOEA SYNDROME			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			

subjects affected / exposed	4 / 35 (11.43%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	5 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ABDOMINAL WOUND DEHISCENCE			
subjects affected / exposed	1 / 35 (2.86%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLICATIONS OF TRANSPLANTED KIDNEY			
subjects affected / exposed	4 / 35 (11.43%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELAYED GRAFT FUNCTION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			
subjects affected / exposed	2 / 35 (5.71%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMOTHORAX			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
LEUKOPENIA			
subjects affected / exposed	1 / 35 (2.86%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOTIC MICROANGIOPATHY			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	3 / 35 (8.57%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PANCREATIC PSEUDOCYST			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS CHRONIC			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	3 / 35 (8.57%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOCAL SEGMENTAL GLOMERULOSCLEROSIS			
subjects affected / exposed	2 / 35 (5.71%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROTEINURIA			
subjects affected / exposed	3 / 35 (8.57%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
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	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERAL NECROSIS			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERIC STENOSIS			
subjects affected / exposed	1 / 35 (2.86%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY INCONTINENCE			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT DISORDER			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINOMA			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

BACTERIAL SEPSIS			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMAN POLYOMAVIRUS INFECTION			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			

subjects affected / exposed	1 / 35 (2.86%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYOMAVIRUS-ASSOCIATED NEPHROPATHY			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUSITIS			
subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 35 (11.43%)	4 / 39 (10.26%)	
occurrences causally related to treatment / all	1 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	2 / 35 (5.71%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 35 (2.86%)	0 / 39 (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	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			

subjects affected / exposed	0 / 35 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tacrolimus Hexal®	Prograf®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 35 (97.14%)	38 / 39 (97.44%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	12 / 35 (34.29%)	20 / 39 (51.28%)	
occurrences (all)	12	21	
General disorders and administration site conditions			
IMPAIRED HEALING			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 35 (8.57%)	7 / 39 (17.95%)	
occurrences (all)	3	7	
PYREXIA			
subjects affected / exposed	1 / 35 (2.86%)	3 / 39 (7.69%)	
occurrences (all)	2	4	
Immune system disorders			
KIDNEY TRANSPLANT REJECTION			
subjects affected / exposed	1 / 35 (2.86%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	4 / 35 (11.43%)	6 / 39 (15.38%)	
occurrences (all)	5	6	
RESTLESSNESS			

subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
SLEEP DISORDER			
subjects affected / exposed	3 / 35 (8.57%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 35 (5.71%)	6 / 39 (15.38%)	
occurrences (all)	2	6	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 35 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
COMPLICATIONS OF TRANSPLANTED KIDNEY			
subjects affected / exposed	5 / 35 (14.29%)	11 / 39 (28.21%)	
occurrences (all)	5	11	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	2 / 35 (5.71%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
PROCEDURAL PAIN			
subjects affected / exposed	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
RENAL LYMPHOCELE			
subjects affected / exposed	4 / 35 (11.43%)	3 / 39 (7.69%)	
occurrences (all)	4	3	
WOUND COMPLICATION			
subjects affected / exposed	16 / 35 (45.71%)	19 / 39 (48.72%)	
occurrences (all)	18	21	
WOUND DEHISCENCE			
subjects affected / exposed	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Cardiac disorders			

SINUS TACHYCARDIA			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 35 (11.43%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
TREMOR			
subjects affected / exposed	3 / 35 (8.57%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 35 (11.43%)	7 / 39 (17.95%)	
occurrences (all)	4	8	
LEUKOCYTOSIS			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
LEUKOPENIA			
subjects affected / exposed	3 / 35 (8.57%)	7 / 39 (17.95%)	
occurrences (all)	5	7	
NEPHROGENIC ANAEMIA			
subjects affected / exposed	5 / 35 (14.29%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
CONSTIPATION			
subjects affected / exposed	2 / 35 (5.71%)	6 / 39 (15.38%)	
occurrences (all)	2	6	
DIARRHOEA			
subjects affected / exposed	5 / 35 (14.29%)	5 / 39 (12.82%)	
occurrences (all)	7	11	
FLATULENCE			

subjects affected / exposed	3 / 35 (8.57%)	4 / 39 (10.26%)	
occurrences (all)	4	4	
HIATUS HERNIA			
subjects affected / exposed	1 / 35 (2.86%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
NAUSEA			
subjects affected / exposed	2 / 35 (5.71%)	5 / 39 (12.82%)	
occurrences (all)	2	5	
VOMITING			
subjects affected / exposed	1 / 35 (2.86%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	2 / 35 (5.71%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
ALOPECIA			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
SCAR PAIN			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
BLADDER PAIN			
subjects affected / exposed	5 / 35 (14.29%)	3 / 39 (7.69%)	
occurrences (all)	5	3	
BLADDER SPASM			
subjects affected / exposed	0 / 35 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
OLIGURIA			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
RENAL FAILURE			

subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
RENAL HYPERTENSION			
subjects affected / exposed	0 / 35 (0.00%)	4 / 39 (10.26%)	
occurrences (all)	0	4	
URINARY RETENTION			
subjects affected / exposed	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Infections and infestations			
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	1 / 35 (2.86%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
CYTOMEGALOVIRUS VIRAEMIA			
subjects affected / exposed	2 / 35 (5.71%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
NASOPHARYNGITIS			
subjects affected / exposed	2 / 35 (5.71%)	3 / 39 (7.69%)	
occurrences (all)	2	4	
PNEUMONIA			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
SEPSIS			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
URINARY TRACT INFECTION			
subjects affected / exposed	6 / 35 (17.14%)	16 / 39 (41.03%)	
occurrences (all)	10	20	
WOUND INFECTION			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			

ACIDOSIS			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
DIABETES MELLITUS			
subjects affected / exposed	3 / 35 (8.57%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	2 / 35 (5.71%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
HYPERKALAEMIA			
subjects affected / exposed	9 / 35 (25.71%)	9 / 39 (23.08%)	
occurrences (all)	10	10	
HYPERLIPIDAEMIA			
subjects affected / exposed	3 / 35 (8.57%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
HYPERPHOSPHATAEMIA			
subjects affected / exposed	1 / 35 (2.86%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
HYPERURICAEMIA			
subjects affected / exposed	3 / 35 (8.57%)	9 / 39 (23.08%)	
occurrences (all)	3	9	
HYPOCALCAEMIA			
subjects affected / exposed	5 / 35 (14.29%)	4 / 39 (10.26%)	
occurrences (all)	5	4	
HYPOKALAEMIA			
subjects affected / exposed	5 / 35 (14.29%)	4 / 39 (10.26%)	
occurrences (all)	5	4	
HYPOMAGNESAEMIA			
subjects affected / exposed	5 / 35 (14.29%)	7 / 39 (17.95%)	
occurrences (all)	5	7	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	3 / 35 (8.57%)	2 / 39 (5.13%)	
occurrences (all)	3	2	

IRON DEFICIENCY			
subjects affected / exposed	0 / 35 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
METABOLIC ACIDOSIS			
subjects affected / exposed	2 / 35 (5.71%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
VITAMIN D DEFICIENCY			
subjects affected / exposed	2 / 35 (5.71%)	6 / 39 (15.38%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	Clarified in page 18 that highly effective contraception methods included total abstinence(when this was in line with the preferred and usual lifestyle of the subject). Whereas periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation and withdrawal were not acceptable methods of contraception. Clarified in page 25 that results from routine blood laboratory evaluation directly assessed before Treatment (i.e. within 24h prior to Treatment) was used instead of further baseline laboratory evaluation. No second assessment implying second drawing of venous blood was to be done. Appendix 4: updated on drugs that may alter tacrolimus concentrations. Appendix 7: visual faculty test- clarified if the investigator suspected neurological symptoms visual faculty test was to be performed. According to investigator's opinion to guarantee patients safety detailed neurological diagnostics conducted by a qualified person (e.g. neurologist) was to be performed. Page 49 Sample Size Calculation: Clarified that since the primary objective in Phase I of this study is the PK-analyses, the number of 27 patients in each arm was required for the PP-PK Set. Randomization was continued until this number of patients was available with complete and evaluable PK-measurements. At the time of this amendment, the drop-out rate was about 30%, that required about 40 patients/arm (= 80 total instead of 30 patients/arm) to be randomized into this study for Phase I. All patients enrolled for phase I of the study were to be included in the total sample size for phase II of the study, given the study continued into phase II.
04 February 2015	In response to German Health Authority's request, the protocol was modified to implement most recent notifications for use of MPA based on the dear health care professional letter (DHCPL) that was sent out for CellCept by Roche on 12 Dec 2014. In detail the study medication stopping rules were adopted to clearly follow the recommendations given in the DHCPL. This information was added to Sections 6.6.3 and toAppendix 16.1.1-Protocol-Appendix 5.
30 March 2015	Phase II of the study was not to be started, rationale for this decision was the high patient drop-out rate and an associated long recruitment timespan. Eighty-one patients were recruited to Phase I and only 45 of the required 54 patients were available for PK analysis. To complete Phase II, 245 (in addition to 81) patients were to be required to achieve calculated sample size. Therefore the protocol was amended to stop recruitment and analyze Phase I patient data of CERL080ADE27 (PK-Phase I). Patients that were still ongoing were scheduled for an end of study (EOS) visit. During this visit patients were informed by the investigator about the endof study and advised about further treatment course.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported