Clinical trial results:
The ONE Study: A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation – Reference Group Trial

Summary

EudraCT number	2011-004301-24
Trial protocol	DE FR IT
Global end of trial date	29 December 2015

Results information

Result version number	v1 (current)
This version publication date	08 January 2017
First version publication date	08 January 2017

Trial information

Trial identification

Sponsor protocol code	ONErgt11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01656135
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Free State of Bavaria, represented by the University of Regensburg, represented by Prof. Edward K. Geissler
Sponsor organisation address	Franz-Josef-Strauss-Allee 11, Regensburg, Germany, 93053
Public contact	Clinical Study Center Surgery, University Hospital Regensburg, +49 9419444895, theonestudy@klinik.uni-regensburg.de
Scientific contact	Clinical Study Center Surgery, University Hospital Regensburg, +49 9419444895, theonestudy@klinik.uni-regensburg.de

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	07 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 December 2015
Global end of trial reached?	Yes
Global end of trial date	29 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the rate of acute kidney graft rejection in the study population under standard immunosuppressive therapy in order to corroborate historical renal transplantation statistics and generate reference ranges for future clinical research within The ONE Study.

The Reference Group Trial is the first clinical trial planned within the context of The ONE Study, an international, non-commercial research project that ultimately aims in subsequent trials to test several alternative GMP cell products as adjunct immunosuppressive treatments in kidney transplantation. Future trials will assess whether immunoregulatory cell infusion could allow for a reduction in the use of pharmacological maintenance therapy in transplant recipients and alleviate the drawbacks associated with traditional immunosuppressive agents.

Protection of trial subjects:

Patients in the Reference Group Trial were treated with a standard immunosuppressive regimen that represented current best practice in preventing renal allograft rejection. Nevertheless, graft rejection is a potentially life-threatening condition. Therefore, no patient was denied anti-rejection therapy that was deemed necessary by the local Investigator. Optimal clinical care for all patients enrolled in the study was paramount. Investigators acted in the patients' best interests at all times by protecting allograft function, even if this resulted in a protocol deviation. Investigators reserved the right to alter the specified regimen in response to intolerable adverse drug reactions or sub-optimal immunosuppression and dose tapering was not mandatory if graft rejection had occurred or if renal dysfunction was observed. Upon completion of the trial protocol for individual patients, immunosuppressive treatment proceeded at the discretion of the local clinical team.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 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	France: 9
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	70
EEA total number of subjects	56

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)	61
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 11th December 2012 and patient recruitment was completed on 25th September 2014. Recruitment took place at six investigative sites in four European countries (Germany, United Kingdom, France and Italy) and at two investigative sites in the USA.

Pre-assignment

Screening details:

A total of 272 patients (across all study sites) were screened against the inclusion and exclusion criteria for the trial. Potential participants were identified by trial Investigators from information readily available during work-up procedures for living-donor kidney transplantation. 70 patients were enrolled.

Period 1

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

Arms

Arm title	Standard immunosuppressive regimen

Arm description:

Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus

Arm type	Experimental
Investigational medicinal product name	Simulect
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day 0: 20mg IV ≤ 2h prior to surgery; Day 4: 20mg IV

Investigational medicinal product name	Prednisolone IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day 0: 500mg IV (250mg pre-op, 250mg intra-op); Day 1: 125mg IV

Investigational medicinal product name	Prednisolone oral
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 2 – 14: 20mg/day oral; Week 3 – 4: 15mg/day oral; Week 5 – 8: 10mg/day oral; Week 9 – 12: 5mg/day oral; Week 13 – 14: 2.5mg/day oral; Week 15 – Study End: Cessation

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard

Routes of administration	Oral use

Dosage and administration details:

Doses were adjusted as necessary to achieve whole blood drug trough levels within the following concentration ranges during the specified time frames:
Day -4 – 14: 3-12ng/ml; Week 3 – 12: 3-10ng/ml; Week 13 – 36: 3-8ng/ml; Week 37 – Study End: 3-6ng/ml

Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Day -1 – 14: 2g/day oral; Day 15 – Study End: 1.5g/day oral (750mg twice daily)

Investigational medicinal product name	Mycophenolic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Doses that are biologically equivalent to those specified for mycophenolate mofetil.

Number of subjects in period 1	Standard immunosuppressive regimen
Started	70
Completed	61
Not completed	9
Consent withdrawn by subject	3
Physician decision	3
Lost to follow-up	1
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus

Reporting group values	Overall trial	Total	
Number of subjects	70	70	
Age categorical			
Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	61	61	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous			
Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy.			
Units: years			
arithmetic mean	48.4		
standard deviation	± 13.3	-	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	50	50	
Ethnicity			
Units: Subjects			
White	62	62	
Asian	7	7	
Other	1	1	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who signed informed consent and received at least one dose of study-specific medication.

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients included in the safety population who underwent kidney transplantation.

Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

All patients included in the safety population who were treated according to protocol specifications (acceptable limits defined in the PP criteria).

Reporting group values	Safety population	Intention-to-treat population	Per-protocol population
Number of subjects	67	66	47
Age categorical			
Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy.			
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)	60	59	43
From 65-84 years	7	7	4
85 years and over	0	0	0
Age continuous			
Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy.			
Units: years			
arithmetic mean	47.6	47.4	47.7
standard deviation	± 13.1	± 13.1	± 12.3
Gender categorical			
Units: Subjects			
Female	18	18	11
Male	49	48	36
Ethnicity			
Units: Subjects			
White	60	59	41
Asian	6	6	5
Other	1	1	1

End points

End points reporting groups

Reporting group title	Standard immunosuppressive regimen
Reporting group description:	
Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who signed informed consent and received at least one dose of study-specific medication.	
Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients included in the safety population who underwent kidney transplantation.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients included in the safety population who were treated according to protocol specifications (acceptable limits defined in the PP criteria).	

Primary: Incidence of biopsy-confirmed acute rejection (BCAR)

End point title	Incidence of biopsy-confirmed acute rejection (BCAR)[1]
End point description:	
Kidney graft biopsies were assessed by a nominated Central Pathologist. A patient was deemed to have reached the primary endpoint only if the Central Pathologist issued a histological confirmation of rejection. Therefore, BCAR required a clinical diagnosis from the local Investigator plus a histopathological confirmation from a for-cause biopsy evaluated by the Central Pathologist. A biopsy was considered to be 'for-cause' if there were overt clinical signs of rejection at the time of sampling. Patients with subclinical rejection detected by a protocol biopsy did not register a primary endpoint. Patients who were diagnosed with acute rejection by the local Investigator, but whose for-cause biopsy did not reveal histopathological evidence of rejection according to the Central Pathologist, also did not register a primary endpoint.	
End point type	Primary
End point timeframe:	
Within 60 weeks following renal transplantation.	

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: This study was a single-armed trial with no comparator arm. Therefore, all endpoints were analysed descriptively and it was not possible to apply any statistical testing to the primary endpoint.

End point values	Intention-to-treat population	Per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	47		
Units: Patients	8	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BCAR episode

End point title	Time to first BCAR episode

End point description:

For each patient who registered a primary endpoint, the time interval between the date of transplantation (“Day 0”) and the date of first BCAR was calculated. The date of first BCAR was defined as the earliest date when both criteria for the primary endpoint (clinical diagnosis and biopsy confirmation from the Central Pathologist) were fulfilled. Therefore, in case the timings of clinical diagnosis and biopsy confirmation did not coincide, the later date was used to measure the time interval. For patients who experienced more than one BCAR, episodes subsequent to the first diagnosis were disregarded. Considering only those patients who registered a primary endpoint, the median and full range are presented here. Time to first BCAR was also analysed by Kaplan-Meier method (results not shown here).

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Intention-to-treat population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Days				
median (full range (min-max))	6 (4 to 326)			

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of first BCAR episode (based on response to treatment)

End point title	Severity of first BCAR episode (based on response to treatment)

End point description:

The severity of BCAR was assessed according to clinical criteria. Investigators were asked to grade the severity of a clinically-diagnosed rejection episode according to the response of the patient to anti-rejection therapy. In the eCRF, severity was classified as: “Spontaneously resolving”, “Glucocorticoid-responsive”, “Responsive to depleting antibody treatment”, “Unresponsive to rescue therapy” or “Not applicable”. The option “Not applicable” was available in case no additional anti-rejection treatment was initiated and the patient could be treated by modulating the doses of the study drugs. For each patient who registered a primary endpoint, severity grades from the first BCAR episode were collected for analysis. For patients who experienced more than one episode of BCAR, episodes subsequent to the first diagnosis were disregarded.

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Intention-to-treat population	Per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	47		
Units: Patients				
Glucocorticoid-responsive	4	4		
Responsive to depleting antibody treatment	3	3		
Not applicable	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of first BCAR episode (based on biopsy histopathology)

End point title	Severity of first BCAR episode (based on biopsy histopathology)

End point description:

The severity of BCAR was evaluated according to the histopathological grading provided by the Central Pathologist. In the eCRF, the options for grading acute rejection pathology were: "Antibody-mediated changes (ABMR)", "Acute T cell-mediated rejection (TCMR) IA", "Acute TCMR IB", "Acute TCMR IIA", Acute TCMR IIB", "Acute TCMR III" and "Borderline changes". These options were not necessarily mutually exclusive. It was possible for the pathologist to select "Mixed ABMR + TCMR" and specify both ABMR and TCMR sub-classifications. For each patient who registered a primary endpoint, severity grades from the first BCAR episode were collected for analysis. For patients who experienced more than one episode of BCAR, episodes subsequent to the first diagnosis were disregarded.

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Intention-to-treat population	Per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	47		
Units: Patients				
Acute TCMR IIA	3	3		
Borderline changes	3	3		
Acute TCMR IA	1	1		
Acute TCMR IB	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse drug reactions (ADRs)

End point title	Incidence of adverse drug reactions (ADRs)

End point description:

An ADR was defined as any AE with a reasonable possibility of a causal relationship to any of the study-specific drugs (basiliximab, IV prednisolone, oral prednisolone, MMF/MPA, tacrolimus), as judged by the reporting Investigator. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. To calculate the prevalence of ADRs, multiple occurrences of the same event (Preferred Term) in one individual were counted only once. For the purposes of this study, graft rejection was exempt from AE reporting.

End point type	Secondary

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Patients				
ADRs	53			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of major infections

End point title	Incidence of major infections

End point description:

Infections were assessed by systematically collecting information on Serious Adverse Events (SAEs) and Adverse Events (AEs) at the regular trial follow-up visits. Viral loads of CMV, EBV and BKV were measured at Visits 4, 5 and 6 or at 4 week intervals after anti-viral chemoprophylaxis had been completed. The patients were also screened for clinical evidence of bacterial, viral and fungal infections at these three time points. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. The number of patients who experienced at least one AE belonging to the MedDRA SOC: "Infections and infestations" is reported here.

End point type	Secondary

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Patients				
MedDRA SOC: Infections and infestations	52			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of neoplasia

End point title	Incidence of neoplasia

End point description:

Neoplasms were assessed by systematically collecting information on Serious Adverse Events (SAEs) and Adverse Events (AEs) at the regular trial follow-up visits. The trial protocol recommended a formal dermatological assessment at Visit 10 (final visit) to screen for signs of skin malignancy. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. The number of patients who experienced at least one AE belonging to the MedDRA SOC: "Neoplasms benign, malignant and unspecified" is reported here.

End point type	Secondary

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Patients				
MedDRA SOC: Neoplasms benign, malignant, unspec.	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For analysis, the observation period for AEs was defined as the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Only these treatment-emergent AEs were included.

Adverse event reporting additional description:

Information on AEs was collected systematically by the study teams at regular trial follow-up visits. It was the responsibility of the Investigator to assess the seriousness and causality of every AE. All reported terms (verbatim) were monitored by source data verification and then coded using MedDRA version 19.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Standard immunosuppressive regimen

Reporting group description:

Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus. For analysis, SAEs and non-serious AEs were summarised for the safety population (N=67).

Serious adverse events	Standard immunosuppressive regimen		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 67 (53.73%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Anticonvulsant drug level therapeutic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Complications of transplanted kidney				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula thrombosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Lymphocele				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Air embolism				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Methaemoglobinaemia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrogenic anaemia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular stent thrombosis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal impairment				
subjects affected / exposed	5 / 67 (7.46%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal artery stenosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cytomegalovirus infection				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus colitis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal oesophagitis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster disseminated				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infected lymphocele				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal abscess				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Polyomavirus-associated nephropathy				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Relapsing fever				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes mellitus				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Standard immunosuppressive regimen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 67 (95.52%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Hypotension			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Lymphocele			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Oedema			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	12		
Pain			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	8		
Reproductive system and breast disorders			

Genital pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Dyspnoea exertional			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Increased bronchial secretion			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Oropharyngeal pain			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	14		
Sleep disorder			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	12		
Investigations			
Blood creatine increased			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Blood pressure increased			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
C-reactive protein increased			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		

Haemoglobin decreased			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	8		
Polyomavirus test positive			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Post procedural haematoma			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	10		
Seroma			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Wound complication			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	16		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 67 (23.88%)		
occurrences (all)	26		
Paraesthesia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Tremor			
subjects affected / exposed	23 / 67 (34.33%)		
occurrences (all)	23		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	10		
Iron deficiency anaemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Leukocytosis			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Leukopenia			
subjects affected / exposed	21 / 67 (31.34%)		
occurrences (all)	26		
Thrombocytopenia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Vertigo			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	13		
Abdominal pain upper			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	23 / 67 (34.33%)		
occurrences (all)	32		
Diarrhoea			
subjects affected / exposed	21 / 67 (31.34%)		
occurrences (all)	34		
Dyspepsia			

subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	12		
Flatulence			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	10		
Nausea			
subjects affected / exposed	24 / 67 (35.82%)		
occurrences (all)	33		
Vomiting			
subjects affected / exposed	14 / 67 (20.90%)		
occurrences (all)	15		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Alopecia			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Night sweats			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	13		
Pruritus			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	8		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Haematuria			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Leukocyturia			

subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Proteinuria			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	10		
Urinary retention			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	13		
Joint swelling			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	11		
Pain in extremity			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	8		
Infections and infestations			
BK virus infection			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	9		
Cytomegalovirus infection			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Cytomegalovirus viraemia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	11		
Nasopharyngitis			

subjects affected / exposed	16 / 67 (23.88%)		
occurrences (all)	20		
Upper respiratory tract infection			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	11		
Urinary tract infection			
subjects affected / exposed	14 / 67 (20.90%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Diabetes mellitus			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Hyperglycaemia			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	9		
Hyperkalaemia			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	11		
Hyperuricaemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	8		
Metabolic acidosis			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Vitamin D deficiency			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	There was only one substantial amendment of the trial protocol during the course of this clinical trial. The trial eligibility criteria were modified to accelerate the rate of patient recruitment, the Visit 3 protocol graft biopsy was changed from mandatory to optional to enable Investigators to perform protocol biopsies at their discretion, the definition of the primary endpoint was simplified, and the overall volume of blood collected from trial patients for a scientific subproject was reduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported