Clinical trial results:
The ONE Study: A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation - M reg Trial

Summary

EudraCT number	2013-000999-15
Trial protocol	DE
Global end of trial date	13 June 2017

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	ONEmreg12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02085629
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Regensburg
Sponsor organisation address	Franz-Josef-Strauss-Allee 11, Regensburg, Germany, 93053
Public contact	Clinical Study Centre Surgery, University Hospital Regensburg, +49 9419444895, theonestudy@klinik.uni-regensburg.de
Scientific contact	Clinical Study Centre 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	03 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2017
Global end of trial reached?	Yes
Global end of trial date	13 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To collect further evidence of the safety of administering donor-derived M reg preparations to living-donor renal transplant recipients. In addition, to determine whether pre-transplant M reg infusion allows some degree of tapering of conventional maintenance immunosuppression within 60 weeks after transplantation. The objective of this study was to evaluate whether the cell-based medicinal product "Mreg_UKR" constitutes a safe and sufficiently promising therapeutic strategy to warrant more extensive development.

Protection of trial subjects:

The Mreg_UKR cell product was released by the manufacturing facility only when all relevant quality control criteria had been met and authorisation was given by the Qualified Person. Mreg_UKR was infused on the surgical intensive care unit at the trial centre, so that patients could be closely monitored and receive emergency medical treatment, if necessary. Patients received prophylactic doses of paracetamol and anti-histamine, and were fully anti-coagulated using a standard sliding-scale heparin infusion to minimise potential adverse reactions to the cell infusion. Low-dose MMF (500 mg/day) was administered from the day of cell infusion until the day prior to organ transplantation (Day -1) as another precautionary measure, intended to minimise the risk of sensitising the recipient to donor alloantigen. Furthermore, patients were tested for donor-specific antibody (DSA) prior to cell infusion and again on Day -1. A negative DSA test result on Day -1 was confirmed before proceeding with organ transplantation.

Graft rejection is a potentially life-threatening condition. Therefore, no patient was denied anti-rejection therapy or any other concomitant treatment 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. Dose tapering was not undertaken if there were signs of graft rejection, evidence of declining renal function or any other clinical contraindication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	7
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

8 patients were enrolled between 24th July 2014 and 23rd February 2016. Mainly owing to manufacturing problems, it was possible to treat only 2 patients with cell therapy. Since the target of treating 16 patients could not be achieved within a reasonable and cost-effective time frame, the trial was prematurely terminated on 3rd December 2018.

Pre-assignment

Screening details:

80 patients were screened for inclusion over the course of four and a half years. Potential participants were identified by trial Investigators from information readily available during work-up procedures for living-donor kidney transplantation. The much stricter rules governing living organ donation led to extended periods without recruitment.

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	Mreg_UKR

Arm description:

Living-donor renal transplant recipients treated with a single infusion of Mreg_UKR seven days prior to transplantation as an adjunct therapy added into a background pharmacological immunosuppressive regimen consisting of prednisolone, MMF/MPA and tacrolimus.

Arm type	Experimental
Investigational medicinal product name	Mreg_UKR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day -7: Single dose of 2.5 - 7.5 x 10^6 cells / kg body weight administered via slow central venous infusion over 10 - 50 minutes.

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

Dosage and administration details:

Day 0: 500 mg IV (250 mg pre-op, 250 mg intra-op); Day 1: 125 mg 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 to 14: 20 mg/day; Week 3 to 4: 15 mg/day; Week 5 to 8: 10 mg/day; Week 9 to 12: 5 mg/day; Week 13 to 14: 2.5 mg/day; Week 15 to 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:

Tacrolimus was initiated within 48 hours prior to transplantation surgery and doses were adjusted as necessary to achieve whole blood drug trough levels within the following concentration ranges during the specified time frames:
≤ 48 hrs pre-op to Day 14: 3-12 ng/ml; Week 3 to 12: 3-10 ng/ml; Week 13 to 36: 3-8 ng/ml; Week 37 to Study End: 3-6 ng/ml.

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

Dosage and administration details:

Low-dose MMF was commenced 7 days prior to transplantation to cover the pre-operative infusion of Mreg_UKR. There was the option to gradually taper doses starting from Week 36, depending on the clinical condition of the patient.
Day -7 to Day -2: 500 mg/day (250 mg twice daily); Day -1 to 14: 2000 mg/day; Week 3 to 36: 1000 mg/day; Week 37 to 40: 750 mg/day; Week 41 to 44: 500 mg/day; Week 45 to 48: 250 mg/day; Week 49 to Study End: Cessation.

Investigational medicinal product name	Mycophenolic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Doses that are biologically equivalent to those specified for mycophenolate mofetil (MMF), if used instead of MMF.

Number of subjects in period 1	Mreg_UKR
Started	8
Completed	2
Not completed	6
Manufactured cell product failed release testing	4
Manufacturing of cell product cancelled	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	8	8	
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			
Adults (18-64 years)	6	6	
From 65-84 years	1	1	
Not recorded	1	1	
Gender categorical			
Units: Subjects			
Female	1	1	
Male	6	6	
Not recorded	1	1	

Subject analysis sets

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

Subject analysis set description:

All patients who signed informed consent, received an infusion of Mreg_UKR and underwent living-donor kidney transplantation.

Reporting group values	Cell-treated population		
Number of subjects	2		
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			
Adults (18-64 years)	2		
From 65-84 years	0		
Not recorded	0		
Gender categorical			
Units: Subjects			
Female	1		
Male	1		
Not recorded	0		

End points

End points reporting groups

Reporting group title	Mreg_UKR

Reporting group description:

Living-donor renal transplant recipients treated with a single infusion of Mreg_UKR seven days prior to transplantation as an adjunct therapy added into a background pharmacological immunosuppressive regimen consisting of prednisolone, MMF/MPA and tacrolimus.

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

Subject analysis set description:

All patients who signed informed consent, received an infusion of Mreg_UKR and underwent living-donor kidney transplantation.

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, even if this coincided with a scheduled protocol biopsy time point. Evidence of subclinical rejection detected in a protocol biopsy did not qualify as a primary endpoint. A clinical diagnosis of acute rejection by the local Investigator, without histopathological confirmation from the Central Pathologist, was also insufficient for 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	Cell-treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Patients	1			

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.

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Cell-treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Days	4			

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 rejection severity 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.

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Cell-treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Episodes				
Spontaneously resolving	0			
Glucocorticoid-responsive	0			
Responsive to depleting antibody treatment	1			
Unresponsive to rescue therapy	0			
Not applicable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of graft loss through rejection

End point title	Incidence of graft loss through rejection

End point description:

Rejections leading to graft loss were defined as episodes of rejection that were reported in the eCRF as "unresponsive to rescue therapy" (severity) and/or "not resolved after 2 weeks" (outcome), if the question "Is this patient dialysis-dependent as a result of this rejection episode?" was answered "Yes".

End point type	Secondary

End point timeframe:

Within 60 weeks following renal transplantation.

End point values	Cell-treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Patients	0			

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 team 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 terms) were monitored by source data verification and then coded using MedDRA version 20.1.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Cell-treated patients

Reporting group description:

Living-donor renal transplant recipients treated with Mreg_UKR cell therapy and a standard immunosuppressive regimen consisting of prednisolone (IV and oral), MMF/MPA, and tacrolimus.

Serious adverse events	Cell-treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Complications of transplant surgery			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt occlusion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Extremity necrosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureteric stenosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cell-treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vascular disorders			
Lymphocele			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Peripheral artery stenosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Catheter site pain			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Impaired healing			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Ovarian cyst			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Nervousness			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Donor specific antibody present			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Polyomavirus test positive			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Wound complication			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	4		
Wound dehiscence			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Complications of transplanted kidney			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Iron deficiency anaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Peritoneal adhesions			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Umbilical hernia			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Urinary retention			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Acute kidney injury			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Bladder discomfort			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Bladder pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	5		
Proteinuria			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Fistula inflammation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Glucose tolerance impaired			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2014	The trial protocol was amended to include additional trial discontinuation criteria based on the occurrence of specific types of Adverse Events, as requested by the concerned ethics committee during the initial clinical trial application.

Notes:

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.

Only two patients were treated prior to premature termination of the study, therefore a statistical analysis of the results is not feasible or appropriate. Equally, the trial endpoints cannot be meaningfully evaluated in a sample size of two.

Notes: