Clinical trial results:
Tacrolimus after rATG and infliximab induction immunosuppression (RIMINI)

Summary

EudraCT number	2015-005346-58
Trial protocol	DE CZ ES
Global end of trial date	31 December 2020

Results information

Result version number	v1
This version publication date	06 November 2022
First version publication date	06 November 2022

Trial information

Trial identification

Sponsor protocol code	RIMINI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04114188
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Prof. Dr. Petra Reinke, Charité - Universitätsmedizin Berlin, +49 030 450 653490, petra.reinke@charite.de
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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	21 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2020
Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

CMV, EBV, BKV PCR monitoring according to protocol will be performed routinely in each center. All patients will receive 100 days valganciclovir prophylaxis at doses adjusted according eGFR and Cotrimoxasol (trimethoprim / sulfamethoxazole) 480mg/day for 6 months.

Protection of trial subjects:

Trial was conducted according to the lnternational Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2016
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	Spain: 5
Country: Number of subjects enrolled	Czechia: 34
Country: Number of subjects enrolled	Germany: 29
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	65
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of study / recruitment start December 1st, 2016
Date of termination of recruitment December 31, 2020
Recruitment at 3 study centers.

Pre-assignment

Screening details:

PRE-TREATMENT VISIT (SCREENING VISIT/ASSESSMENT at POD 0, inclusion/exclusion criteria will be verified, written informed consent will be obtained, baseline examination and several immune monitoring platforms will be assessed
1098 Subjects assessed for eligibility
1029 Subjects excluded
69 Subjects were allocated
2 no intervention

Period 1

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

Arms

Arm title	Tacrolimus Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	INFLIXIMAB
Investigational medicinal product code	
Other name	SUB02681MIG
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5mg/kg b.w. – once daily on day 2
Intravenous infusion

Investigational medicinal product name	Thymoglobulin
Investigational medicinal product code	
Other name	ANTITHYMOCYTE IMMUNOGLOBULIN, SUB128808
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.5mg/kg b.w. – once daily on day0 and on day1
intravenous infusion

Investigational medicinal product name	TACROLIMUS
Investigational medicinal product code	
Other name	SUB10797MIG
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

before surgery 0,1 mg/kg and 0.2mg/kg after surgery
10-15 ng/mL, POD1-POD13
5-8 ng/mL POD 14-90
4-6 ng/mL POD >90
Tacrolimus is recommended as routine post-transplant immunosuppression. Tacrolimus doses will be modified according to through levels as recommended by manufacturer.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	SUB10018MIG
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

500 mg - once daily on day0 and on day1 as intravenous infusion From day 2 oral administration, dose will be slowly tapered down to 5 mg at the POD 7

Number of subjects in period 1	Tacrolimus Group
Started	68
Completed	68

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	68	68	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 49.6 ± 10.2	 -	
Gender categorical Units: Subjects			
Female	12	12	
Male	56	56	
Race Units: Subjects			
Caucassian	68	68	

End points

End points reporting groups

Reporting group title	Tacrolimus Group

Reporting group description: -

Primary: efficacy failure of the induction regimen

End point title	efficacy failure of the induction regimen[1]

End point description:

acute rejection, graft loss or poor graft function defined as eGFR<40 ml/min.
In total, 22 out of 67 KTRs (32.84%) have experienced efficacy failure during the 12 months study follow-up, the upper-bound of the exact one-sided 95% confidence interval is 43.47%. This result fulfills the predefined criteria of efficacy failure rate of no more than 40% with an upper-bound of the exact one-sided 95% confidence interval of no more than 50%.

End point type	Primary

End point timeframe:

12 months

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 result fulfills the predefined criteria of efficacy failure rate of no more than 40% with an upper-bound of the exact one-sided 95% confidence interval of no more than 50%.

End point values	Tacrolimus Group			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Subjects				
graft loss	4			
acute rejection	11			
persistent poor graft function	13			
acute rejection+poor graft function	5			
acute rejection+ graft failure	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation and Remain of study treatment by 12 months posttransplant

End point title	Discontinuation and Remain of study treatment by 12 months posttransplant

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Tacrolimus Group			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Subjects				
remaind on the study protocol	53			
permanent discontinuation	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of acute and chronic lesions

End point title	Incidence of acute and chronic lesions

End point description:

End point type	Secondary

End point timeframe:

12 months posttranplant

End point values	Tacrolimus Group			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Subjects				
chronic T-cell mediated rejection grade II	1			
chronic active antibody-mediated rejection	1			
poor graft function by antibody-mediated rejection	2			
acute rejection	11			

Statistical analyses

No statistical analyses for this end point

Secondary: protocolar biopsy

End point title	protocolar biopsy

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Tacrolimus Group			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Subjects				
acute/chronic rejection lesions	5			
active antibody mediated rejection	2			
chronic active antobody mediated rejection	2			
acute T-cell mediated rejection IIA	1			
not performed due to graft failure	4			
patient refusal	4			
organization difficulties	12			
no kidney tissues	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Tacrolimus Group

Reporting group description: -

Serious adverse events	Tacrolimus Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 67 (61.19%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
lung carcinoma with metastasis sus			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
vasoproliferative retinal tumor			
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			
coronary 3 vessel heart disease			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hypertensiv pulmonary edema			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

pulmonary embolism				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
relapsing dialysis shunt thrombosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis of lower artery og the graft kidney				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
thrombosis vena iliaca externa right				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ventricular fibrillation				
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				
aneurysmal shunt vein				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhagie				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
active humoral rejection				

subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
proof of donor-specific antibodies HLA class II				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
delayed graft function				
subjects affected / exposed	5 / 67 (7.46%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
graft non-function				
subjects affected / exposed	5 / 67 (7.46%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Hernia umbilicalis incarcerata				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
nephrectomy bleeding cyst kidney right side				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hemorrhage after biopsy				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right testide hematoma- surgical intervention				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
hypoxic brain damage, inauspiciuos prognosis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Leucopenia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
incomplete retinal central vein occlusion right ey			
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			
ulcerous stomach with hemorrhagic oozing			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
unclear abdominal discomforts			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
wound healing disease			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
acute allograft Rejection Banff grade IA and IB			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

acute kidney failure with diuretic overdose				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
acute allograft Rejection Banff grade IIA and IIB				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
graft function worsening				
subjects affected / exposed	9 / 67 (13.43%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
hydronephrosis				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Incipient sepsis - probably source - urinary tract				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
increased creatinine				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
acute Chondrocalcinosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
contusion trauma				

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			
CMV colitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Increasing viral load of polyomavirus in the blood			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
infected postoperative retroperitoneal haematoma			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
phlebitis with abces			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
urinary tract infection			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Diabetic foot			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gout			
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: 1 %

Non-serious adverse events	Tacrolimus Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 67 (100.00%)		
Injury, poisoning and procedural complications			
postoperative pain/surgery pain			
subjects affected / exposed	51 / 67 (76.12%)		
occurrences (all)	52		
Vascular disorders			
increased blood pressure/hypertension			
subjects affected / exposed	22 / 67 (32.84%)		
occurrences (all)	29		
Cardiac disorders			
edema (leg)			
subjects affected / exposed	22 / 67 (32.84%)		
occurrences (all)	25		
Nervous system disorders			
headache			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
worsening anemia			
subjects affected / exposed	13 / 67 (19.40%)		
occurrences (all)	14		
Leukopenia			

subjects affected / exposed occurrences (all)	11 / 67 (16.42%) 12		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomitting subjects affected / exposed occurrences (all) nausea subjects affected / exposed occurrences (all) obstipation subjects affected / exposed occurrences (all)	 11 / 67 (16.42%) 14 12 / 67 (17.91%) 15 10 / 67 (14.93%) 14 13 / 67 (19.40%) 15		
Respiratory, thoracic and mediastinal disorders dyspnoe subjects affected / exposed occurrences (all)	 6 / 67 (8.96%) 10		
Renal and urinary disorders delayed graft function subjects affected / exposed occurrences (all) leukocyturia subjects affected / exposed occurrences (all) increased creatinine subjects affected / exposed occurrences (all) dysuria subjects affected / exposed occurrences (all)	 13 / 67 (19.40%) 13 7 / 67 (10.45%) 7 11 / 67 (16.42%) 16 18 / 67 (26.87%) 18		
Psychiatric disorders sleeping disorder subjects affected / exposed occurrences (all)	 11 / 67 (16.42%) 13		

Infections and infestations			
BK-Virus,CMV	Additional description: 4 Subject with Bk-Virus; 4 Patients with CMV		
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
increased CRP			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	12		
fever/ increased body temerature			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Urinary Tract Infection			
subjects affected / exposed	17 / 67 (25.37%)		
occurrences (all)	25		
upper tract, Cough, Brochitis, Pneumonia			
subjects affected / exposed	13 / 67 (19.40%)		
occurrences (all)	15		
common cold			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	13		
Metabolism and nutrition disorders			
Hypocalcemia			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	8		
Hypouricemia			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	12		
Hyperkalemia			
subjects affected / exposed	25 / 67 (37.31%)		
occurrences (all)	25		
Hyperglycemia			
subjects affected / exposed	16 / 67 (23.88%)		
occurrences (all)	16		
acidose			
subjects affected / exposed	20 / 67 (29.85%)		
occurrences (all)	21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2017	Change of the protocol; Further specification of an exclusion criterion, with respect to safety reasons

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported