Clinical trial results:
A randomized open-label trial to evaluate the cardiovascular risk in stable renal allograft recipients on a ciclosporin A (CsA) based regimen monitored either by residual expression of nuclear factor of activated T-cells (NFAT) – regulated genes or CsA trough levels

Summary

EudraCT number	2011-003547-21
Trial protocol	DE
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	21 May 2022
First version publication date	21 May 2022

Trial information

Trial identification

Sponsor protocol code	RCHD–CsA1004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Renal Center Heidelberg
Sponsor organisation address	Im Neuenheimer Feld 162, Heidelberg, Germany, 69120
Public contact	Clinical Trials Information, Renal Clinic Heidelberg (Nephrology Unit, University Hospital Heidelberg), +49 622191120, info@nierenzentrum-heidelberg.com
Scientific contact	Clinical Trials Information, Renal Clinic Heidelberg (Nephrology Unit, University Hospital Heidelberg), +49 622191120, info@nierenzentrum-heidelberg.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The comparison of a CsA-based immunosuppression either monitored by CsA trough levels or NFAT-regulated gene expression concerning the cardiovascular risk

Protection of trial subjects:

Assess renal allograft function
Assess Quality of Life assessed by the ESRD SCLTM questionnaire and SF12 questionaire

Background therapy:

triple drug immunosuppressive therapy consisting of mycophenolate and steroids in addition to ciclosporin A

Evidence for comparator:

Standard Therapy: Ciclosporin A adapted to Ciclosporin A trough levels (comparator).
Ciclosporin A is an approved drug and used in clinical practice since more than 30 years.
Using Ciclosporin A trough levels is the standard procedure for monitoring and adaption of Ciclosporin A dosages.

Actual start date of recruitment	15 August 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: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

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)	44
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients of the renal transplant outpatient clinic at the Renal Center Heidelberg (Department of Nephrology University Hospital Heidelberg) suitable to participate in the study were asked to participate and enrolled consecutively.

Pre-assignment

Screening details:

Inclusion criteria specified that patients were to be 18 years or older, have received a renal allograft from a deceased or living donor at least 6 months before study entry, and have stable renal allograft function, receiving Ciclosporin A and mycophenolate. Key exclusion criteria included history of biopsy-proven acute rejection.

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

All patients were blinded to treatment procedures (not knowing the method of Ciclosporin A monitoring and adaption).

Arms

Are arms mutually exclusive?	No
Arm title	Arm A

Arm description:

CsA adapted to standard C0 levels (80-150µg/L)

Arm type	Active comparator
Investigational medicinal product name	Ciclosporin A
Investigational medicinal product code	
Other name	Sandimmun ostoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

adapted to Ciclosporin A trough level (80-150 ug/L)

Arm title	Arm B

Arm description:

CsA adapted to residual NFAT-regulated gene expression (15 –30%) if CsA C0 ≥ 30 µg/L

Arm type	Experimental
Investigational medicinal product name	Ciclosporin A
Investigational medicinal product code	
Other name	Sandimmun ostoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

adapted to NFAT-regulated gene expression (15-30%) with Ciclosporin A trough level >30 ug/L.

Number of subjects in period 1	Arm A	Arm B
Started	27	28
Completed	27	26
Not completed	0	2
Consent withdrawn by subject	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
CsA adapted to standard C0 levels (80-150µg/L)	
Reporting group title	Arm B
Reporting group description:	
CsA adapted to residual NFAT-regulated gene expression (15 –30%) if CsA C0 ≥ 30 µg/L	

Reporting group values	Arm A	Arm B	Total
Number of subjects	27	28	55
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	51.1	50.9	
standard deviation	± 14.0	± 12.3	-
Gender categorical Units: Subjects			
Female	13	6	19
Male	14	22	36

End points

End points reporting groups	
Reporting group title	Arm A
Reporting group description: CsA adapted to standard C0 levels (80-150µg/L)	
Reporting group title	Arm B
Reporting group description: CsA adapted to residual NFAT-regulated gene expression (15 –30%) if CsA C0 ≥ 30 µg/L	

Primary: change in pulse wave velocity from baseline to month 6	
End point title	change in pulse wave velocity from baseline to month 6
End point description: change of PWV from baseline to month 6	
End point type	Primary
End point timeframe: 6 months	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: m/s				
arithmetic mean (standard deviation)	0.4 (± 1.4)	-1.7 (± 2.0)		

Statistical analyses

Statistical analysis title	primary end point
Statistical analysis description: The null hypothesis was that the change in PWV between baseline and month 6 was the same in both treatment arms. The primary analysis was performed on the intention-to-treat population. Analysis of covariance (ANCOVA) was applied, with treatment, age, baseline PWV and eGFR as covariates.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
6 months (baseline to month 6)	
Adverse event reporting additional description:	
all adverse events occurring from baseline to month 6 were collected	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Standard monitoring by Ciclosporin A trough level (comparator, standard)	
Reporting group title	Arm B
Reporting group description:	
Ciclosporin A adapted by NFAT-regulated gene expression (experimental group)	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)	9 / 26 (34.62%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Infection			
subjects affected / exposed	4 / 27 (14.81%)	6 / 26 (23.08%)	
occurrences causally related to treatment / all	1 / 5	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 27 (59.26%)	15 / 26 (57.69%)	
General disorders and administration site conditions			
infection			

subjects affected / exposed	11 / 27 (40.74%)	8 / 26 (30.77%)	
occurrences (all)	20	13	
calcineurin inhibitor related			
subjects affected / exposed	16 / 27 (59.26%)	7 / 26 (26.92%)	
occurrences (all)	30	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

no limitations and caveats

Notes: