Clinical trial results:
Etude prospective, multicentrique, randomisée, en double-aveugle, contrôlée à groupes parallèles, visant à évaluer la balance bénéfice-risque du sevrage progressif d'un inhibiteur de la calcineurine (Tacrolimus) chez des patients transplantés depuis plus de 4 ans et cliniquement sélectionnés

Summary

EudraCT number	2010-019574-33
Trial protocol	FR
Global end of trial date	20 May 2015

Results information

Result version number	v1 (current)
This version publication date	29 December 2017
First version publication date	29 December 2017

Trial information

Trial identification

Sponsor protocol code	BRD 09/7-D

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01292525
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Nantes
Sponsor organisation address	5 allée de l'Ile Gloriette, Nantes, France, 44093
Public contact	Pr GIRAL, Coordinator Investigator, CHU Nantes, +33 0253482835, magali.giral@chu-nantes.fr
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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	08 March 2016
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

Démontrer le bénéfice du sevrage du Tacrolimus (Prograf) sur la fonction rénale des patients un an après la fin de la période de sevrage

Protection of trial subjects:

Very close follow-up of the patients with biological analysis and biopsies if necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2011
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	France: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Renal transplant patients for more than 4 years and clinically selected

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus

Arm description:

A control group continued conventional therapy, Tacrolimus (Prograf®) ("control" group) and was followed in parallel group "withdrawal" that will stop treatment with Tacrolimus (Prograf®).

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

Dosage and administration details:

The dosage of Tacrolimus was adjusted to maintain a Tacrolimus blood concentration of between 5 and 10 ng / ml.

Arm title	Withdrawal of Tacrolimus

Arm description:

Patients randomized to the "withdrawal" group began the protocol with their usual dose of Tacrolimus (Prograf®) (initial dose). The initial dose of tacrolimus
(Prograf®) was reduced by one third at visit 3 (day 0) and again a third visit 5 (J60). The complete withdrawal Tacrolimus (Prograf®) began to visit 7 (J120). The withdrawal of Tacrolimus (Prograf®) was obtained in four months. Monitoring of all patients lasted 17 months in total from the screening visit, which corresponded to 12 months after complete withdrawal of Tacrolimus (Prograf®) for patients in the "withdrawal" group.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Buccal use

Dosage and administration details:

Patients randomized to the "withdrawal" group began the protocol with their usual dose of Tacrolimus (Prograf®) (initial dose). The initial dose of tacrolimus
(Prograf®) was reduced by one third at visit 3 (day 0) and again a third visit 5 (J60). The complete withdrawal Tacrolimus (Prograf®) began to visit 7 (J120). The withdrawal of Tacrolimus (Prograf®) was obtained in four months. Monitoring of all patients lasted 17 months in total from the screening visit, which corresponded to 12 months after complete withdrawal of Tacrolimus (Prograf®) for patients in the "withdrawal" group.

Number of subjects in period 1	Tacrolimus	Withdrawal of Tacrolimus
Started	5	5
Completed	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus
Reporting group description:	
A control group continued conventional therapy, Tacrolimus (Prograf®) ("control" group) and was followed in parallel group "withdrawal" that will stop treatment with Tacrolimus (Prograf®).	
Reporting group title	Withdrawal of Tacrolimus
Reporting group description:	
Patients randomized to the "withdrawal" group began the protocol with their usual dose of Tacrolimus (Prograf®) (initial dose). The initial dose of tacrolimus (Prograf®) was reduced by one third at visit 3 (day 0) and again a third visit 5 (J60). The complete withdrawal Tacrolimus (Prograf®) began to visit 7 (J120). The withdrawal of Tacrolimus (Prograf®) was obtained in four months. Monitoring of all patients lasted 17 months in total from the screening visit, which corresponded to 12 months after complete withdrawal of Tacrolimus (Prograf®) for patients in the "withdrawal" group.	

Reporting group values	Tacrolimus	Withdrawal of Tacrolimus	Total
Number of subjects	5	5	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	4	9
From 65-84 years	0	1	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	1	2
Male	4	4	8

End points

End points reporting groups

Reporting group title	Tacrolimus

Reporting group description:

A control group continued conventional therapy, Tacrolimus (Prograf®) ("control" group) and was followed in parallel group "withdrawal" that will stop treatment with Tacrolimus (Prograf®).

Reporting group title	Withdrawal of Tacrolimus

Reporting group description:

Patients randomized to the "withdrawal" group began the protocol with their usual dose of Tacrolimus (Prograf®) (initial dose). The initial dose of tacrolimus
(Prograf®) was reduced by one third at visit 3 (day 0) and again a third visit 5 (J60). The complete withdrawal Tacrolimus (Prograf®) began to visit 7 (J120). The withdrawal of Tacrolimus (Prograf®) was obtained in four months. Monitoring of all patients lasted 17 months in total from the screening visit, which corresponded to 12 months after complete withdrawal of Tacrolimus (Prograf®) for patients in the "withdrawal" group.

Primary: Renal function

End point title	Renal function[1]

End point description:

The primary endpoint was the improvement of renal function one year after complete withdrawal of Tacrolimus (Prograf®) assessed by measuring the glomerular filtration rate (GFR) calculated by the dosage of cystatin C according to the equation Bricon. The DFG was compared between times J-30 and J480 (1 year after the withdrawal).

End point type	Primary

End point timeframe:

One year after complete withdrawal of Tacrolimus.

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: Due to the premature discontinuation of the study after the inclusion of 16 patients (including 10 randomized patients), it was not possible to statistically evaluate the primary endpoint of improvement in renal function one year after complete weaning of Tacrolimus (Prograf®) evaluated by measuring the Glomerular Filtration Rate (GFR) calculated by the cystatin C assay according to the Le Bricon equation.

End point values	Tacrolimus	Withdrawal of Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: mL/min				
number (not applicable)	5	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of the consent form until the end of follow-up for the non-serious adverse events and until resolution for the serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Tacrolimus
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Tacrolimus	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	5 / 5 (100.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Antibody positive			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
IgA nephropathy			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tacrolimus	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	
occurrences (all)	1	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2012	The main changes to the protocole are : - Addition of a new center, - Increase of the inclusion period to 36 months, - Modification of too restrictive inclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27367750