Clinical trial results:
ENSAYO CLÍNICO DE FASE II, ABIERTO, UNICÉNTRICO, PILOTO PARA EVALUAR LAS CARACTERÍSTICAS FARMACOCINÉTICAS, SEGURIDAD Y TOLERABILIDAD, TRAS LA CONVERSIÓN DE UN RÉGIMEN INMUNOSUPRESOR CON PROGRAF® A TACROLIMUS DE LIBERACIÓN PROLONGADA (ADVAGRAF®) EN PACIENTES CON TRASPLANTE PULMONAR ESTABLE

Summary

EudraCT number	2009-015863-15
Trial protocol	ES
Global end of trial date	29 August 2011

Results information

Result version number	v1 (current)
This version publication date	29 December 2021
First version publication date	29 December 2021

Trial information

Trial identification

Sponsor protocol code	TX-PULMON09

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall dHebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, joaquin.lopez.soriano@vhir.org
Scientific contact	Dr Antonio Roman, VHIR, aroman@vhebron.net

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	29 August 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determinar y comparar el perfil farmacocinético de tacrolimus en pacientes con trasplante de pulmón estable tras la conversión 1:1 de tacrolimus (Prograf®) a tacrolimus de liberación prolongada (Advagraf®).
The purpose of this study was to establish and compare the PK profile of tacrolimus in stable adult lung transplantation patients before and after conversion (1:1) from twice-daily to once-daily dosing.

Protection of trial subjects:

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. Each patient gave written informed consent before enrolment in the study. Corticosteroids were started in the operating room and before initiating lung perfusion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2010
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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The inclusion criteria were adult LT patients, more than 180 days of post-LT follow-up, and stable tacrolimus dose with C0 between 5 and 15 ng/mL

Period 1

Period 1 title	TAC-BID
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	TACROLIMUS TWICE

Arm description: -

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

Dosage and administration details:

Tacrolimus dosage was modified as follows: mean daily dose of TAC BID before switching (day -14) was 4.8+/-2.2 mg. After conversion to QD, mean daily dose was increased to 5.2+/-2.6, 5.4+/-3.0, and 5.6+/-3.1 mg on days +60, +90 and +180, respectively.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Corticosteroids were started in the operating room and before initiating lung perfusion. The initial dose was 10 mg/kg followed by 6 mg/kg the first postoperative day. This drug was decreased to 0.5 mg/kg during the first week, and dose ranged from 0.5 to 0.1 mg/kg per day thereafter

Investigational medicinal product name	Antimetabolite drugs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mycophenolate mofetil [MMF], mycophenolic acid, or azathioprine at the operation room

Arm title	TACROLIMUS SINGLE DOSE

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Buccal use

Dosage and administration details:

Tacrolimus dosage was modified as follows: mean daily dose of TAC BID before switching (day -14) was 4.8+/-2.2 mg. After conversion to QD, mean daily dose was increased to 5.2+/-2.6, 5.4+/-3.0, and 5.6+/-3.1 mg on days +60, +90 and +180, respectively.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Corticosteroids were started in the operating room and before initiating lung perfusion. The initial dose was 10 mg/kg followed by 6 mg/kg the first postoperative day. This drug was decreased to 0.5 mg/kg during the first week, and dose ranged from 0.5 to 0.1 mg/kg per day thereafter

Investigational medicinal product name	Antimetabolite drugs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mycophenolate mofetil [MMF], mycophenolic acid, or azathioprine at the operation room

Number of subjects in period 1	TACROLIMUS TWICE	TACROLIMUS SINGLE DOSE
Started	19	19
Completed	19	19

Period 2

Period 2 title	TAC-QD
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	TAC QD

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Buccal use

Dosage and administration details:

Tacrolimus dosage was modified as follows: mean daily dose of TAC BID before switching (day -14) was 4.8+/-2.2 mg. After conversion to QD, mean daily dose was increased to 5.2+/-2.6, 5.4+/-3.0, and 5.6+/-3.1 mg on days +60, +90 and +180, respectively.

Number of subjects in period 2	TAC QD
Started	19
Completed	19

Baseline characteristics

Reporting groups	
Reporting group title	TACROLIMUS TWICE
Reporting group description: -	
Reporting group title	TACROLIMUS SINGLE DOSE
Reporting group description: -	

Reporting group values	TACROLIMUS TWICE	TACROLIMUS SINGLE DOSE	Total
Number of subjects	19	19	19
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	19
Gender categorical Units: Subjects			
Female	9	9	9
Male	10	10	10

End points

End points reporting groups

Reporting group title	TACROLIMUS TWICE
Reporting group description: -	
Reporting group title	TACROLIMUS SINGLE DOSE
Reporting group description: -	
Reporting group title	TAC QD
Reporting group description: -	

Primary: AUC 24h

End point title	AUC 24h
End point description:	
End point type	Primary
End point timeframe:	
24 hours	

End point values	TACROLIMUS TWICE	TACROLIMUS SINGLE DOSE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: unit(s)				
arithmetic mean (standard deviation)	279.8 (± 57.7)	278.7 (± 52.5)		

Statistical analyses

Statistical analysis title	AUC 0-24
Comparison groups	TACROLIMUS TWICE v TACROLIMUS SINGLE DOSE
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9217
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Wilcoxon test

Secondary: Cmax 0-24

End point title	Cmax 0-24
End point description:	
End point type	Secondary

End point timeframe:
24 hours

End point values	TACROLIMUS TWICE	TACROLIMUS SINGLE DOSE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	20.1 (± 4.0)	19.1 (± 3.2)		

Statistical analyses

Statistical analysis title	Cmax 0-24
Comparison groups	TACROLIMUS TWICE v TACROLIMUS SINGLE DOSE
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7482
Method	Schuirmann double t-test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Total adverse events

Reporting group description: -

Serious adverse events	Total adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary sepsis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 19 (5.26%)		
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	Total adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Transient ischaemic attack			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Libido decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Peripheral oedema			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Eye disorders			
Cataract			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 4 / 19 (21.05%) 4		
Respiratory, thoracic and mediastinal disorders Bronchitis subjects affected / exposed occurrences (all)	 5 / 19 (26.32%) 5		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Fungal infection subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Renal and urinary disorders Pyelonephritis subjects affected / exposed occurrences (all) Cholecystitis acute subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders Movement disorder subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Infections and infestations Papilloma subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Metabolism and nutrition disorders			

Weight gain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

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.

A potential limitation of the study design is the short follow-up period (6 months), which is insufficient to show differences in efficacy between TAC BID and TAC QD. Also of note was the exclusion of patients with cystic fibrosis

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24492423