



## Clinical trial results:

### The influence of CYP3A5 and ABCB1 genotype on the pharmacokinetics of twice daily Tacrolimus and Advagraf

#### Summary

EudraCT number	2009-013461-25
Trial protocol	GB
Global end of trial date	16 June 2014

#### Results information

Result version number	v1 (current)
This version publication date	23 December 2021
First version publication date	23 December 2021
Summary attachment (see zip file)	Final Report (Advagraf study_End of Study Report Template_V4.0 25.11.2019 (3).pdf) Presentation (Influence of CYP3A5 and ABCB1 Genotypes on Pharmacokinetics of Immediate and Prolonged Release Tacrolimus Preparations.pdf)

#### Trial information

#### Trial identification

Sponsor protocol code	UK-02-RG-194_09.0098
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#### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	St Georges University of London
Sponsor organisation address	Cranmer Terrace, London, United Kingdom, SW17 0QT
Public contact	Prof MacPhee, St Georges University of London, imacphee@sgul.ac.uk
Scientific contact	Prof MacPhee, St Georges University of London, imacphee@sgul.ac.uk

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 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2014
Global end of trial reached?	Yes
Global end of trial date	16 June 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- 1) Determine the influence of CYP3A5 and ABCB1 genotypes on Advagraf pharmacokinetics
- 2) Compare the influence of these genotypes on the comparison between Prograf and Advagraf pharmacokinetics

Protection of trial subjects:

none

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 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	United Kingdom: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	64
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Of 75 stable kidney transplant patients who were screened and considered eligible for participation, 11 withdrew before the study began. Therefore, 64 patients enrolled.

### Pre-assignment

Screening details:

Of 75 stable kidney transplant patients who were screened and considered eligible for participation, 11 withdrew before the study began. Therefore, 64 patients enrolled.

### Period 1

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

Blinding implementation details:

open labelled study

### Arms

Arm title	Tacrolimus
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Arm description:

All participants received Tacrolimus for 2 weeks

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

twice a day for 2 weeks

<b>Number of subjects in period 1</b>	Tacrolimus
Started	64
Completed	64

### Period 2

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

Blinding implementation details:

open labelled

**Arms**

<b>Arm title</b>	Advagraf
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Arm description:

All participants received Advagraf

Arm type	Experimental
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Investigational medicinal product name	Advagraf
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

once a day for 2 weeks

<b>Number of subjects in period 2</b>	Advagraf
Started	64
Completed	64

## Baseline characteristics

### Reporting groups

Reporting group title | period 1

Reporting group description: -

<b>Reporting group values</b>	period 1	Total	
Number of subjects	64	64	
Age categorical Units: Subjects			
Adults (18-64 years)	64	64	
Age continuous Units: years			
arithmetic mean	55		
standard deviation	± 13	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	43	43	
Number of participants with Immunosuppression at baseline Units: Subjects			
Tacrolimus_Prograf	48	48	
Tacrolimus_Adoport®	16	16	

## End points

### End points reporting groups

Reporting group title	Tacrolimus
Reporting group description:	All participants received Tacrolimus for 2 weeks
Reporting group title	Advagraf
Reporting group description:	All participants received Advagraf
Subject analysis set title	CYP3A5 Expressers
Subject analysis set type	Sub-group analysis
Subject analysis set description:	Individuals possessing at least one CYP3A5*1 allele (CYP3A5-expressers)
Subject analysis set title	CYP3A5*1 non-expressers
Subject analysis set type	Sub-group analysis
Subject analysis set description:	CYP3A5*3/*3 carriers (CYP3A5 non-expressers)

### Primary: Tacrolimus PK parameters - DOSE - according to their CYP3A5\*3 genotypes

End point title	Tacrolimus PK parameters - DOSE - according to their CYP3A5*3 genotypes
End point description:	
End point type	Primary
End point timeframe:	2 weeks

End point values	CYP3A5 Expressers	CYP3A5*1 non-expressers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: mg/kg/day				
arithmetic mean (standard deviation)	0.11 ( $\pm$ 0.05)	0.05 ( $\pm$ 0.03)		

### Statistical analyses

Statistical analysis title	Dose
Comparison groups	CYP3A5 Expressers v CYP3A5*1 non-expressers
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

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**Primary: Tacrolimus PK parameters - Cmax - according to their CYP3A5\*3 genotypes**

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End point title	Tacrolimus PK parameters - Cmax - according to their CYP3A5*3 genotypes
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End point description:

End point type	Primary
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End point timeframe:

2 weeks

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<b>End point values</b>	CYP3A5 Expressers	CYP3A5*1 non-expressers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: µg/L/mg/Kg				
arithmetic mean (standard deviation)	19.1 (± 10.6)	33.5 (± 13.8)		

**Statistical analyses**

<b>Statistical analysis title</b>	Cmax
Comparison groups	CYP3A5 Expressers v CYP3A5*1 non-expressers
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

4 weeks

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

All participants

<b>Serious adverse events</b>	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No serious adverse event was reported

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported