Clinical trial results:
A Multi Center, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Days after Transplantation

Summary

EudraCT number	2012-001909-24
Trial protocol	NL
Global end of trial date	15 September 2015

Results information

Result version number	v1 (current)
This version publication date	11 August 2021
First version publication date	11 August 2021
Summary attachment (see zip file)	A Multi Center, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Days after Transplantation (study report Spartacus_ NL40432.041.12_A Multi Center, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation.pdf) analysis unbound tacrolimus concentrations (2016 Stienstra TDM.pdf) NONMEM model unbound tacrolimus concentrations (Sikma CPKA 2019.pdf) European Journal of Drug Metabolism and Pharmacokinetics (2020) 45:123–134 (SIkma EJDMP 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	Spartacus/007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	National Trial registration: NTR3912

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 CX
Public contact	Dutch Poisons Information Center, University Medical Center Utrecht, 0031 8875585611, m.a.sikma@umcutrecht.nl
Scientific contact	Dutch Poisons Information Center, University Medical Center Utrecht, 0031 8875585611, m.a.sikma@umcutrecht.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	15 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To show that the variability of whole blood trough and unbound plasma tacrolimus concentrations during the first 6 days post transplantation is larger than the variability of tacrolimus concentrations in stable clinical situation.

Protection of trial subjects:

This study was an observational study.

Background therapy:

Tacrolimus is an immunosuppressant used in solid organ transplantation for prevention of rejection.

Evidence for comparator:

No comparator.

Actual start date of recruitment	06 May 2013
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	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirty transplantation patients are studied. Ten heart transplant recipients and 20 lung transplant recipients, of which 10 cystic fibrosis patients, are analyzed as planned.

Pre-assignment

Screening details:

Each heart and lung transplantation patient fulfilling all of the inclusion criteria and none of the exclusion criteria are included after the nature and purpose of the investigation is explained to them, and they all have signed a study specific informed consent form.

Pre-assignment period milestones

Number of subjects started	30
Intermediate milestone: Number of subjects	inclusion: 30
Number of subjects completed	30

Period 1

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

Arms

Arm title	baseline characteristics

Arm description:

baseline characteristics

Arm type	observation
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	L04AD02
Other name	prograft
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The tacrolimus dose is adjusted by the attending physicians according to the trough tacrolimus blood concentration measured the previous day at 6 am.

Number of subjects in period 1	baseline characteristics
Started	30
Completed	30

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

Arms	
Arm title	end data
Arm description: Observation of tacrolimus blood concentrations	
Arm type	observation
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	end data
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	baseline characteristics
Reporting group description:	
Mean age 43 (IQR 34;60), Male 15 (50%), bodyweight 73.5 kg (IQR 61;86), heart transplants 10 (ischemic cardiomyopathy 5, non-ischemic cardiomyopathy 5), lung transplants 20 (Cystic fibrosis 10 , COPD 4, ILD 6, Double lung transplantation 18), mean SOFA score 7 (IQR 4;12), SIRS at least once between days 1 and 6 30 (100%), SIRS duration (days) 4.5 (3;6), Gut dysmotility frequency 29 (96.7%), percentage Ileus at least once between days 1 and 6 27 (90%), Ileus duration 2 days (IQR 2; 3), Diarrhea at least once between days 1 and 6 18 (60%), Diarrhea duration 1 day (IQR 0;2), Postoperative ECMO frequency 8 (27%), Postoperative ECMO duration (days) 4 (2;6). Tacrolimus, Tacrolimus C12 h (ng/ml) (min–max) 9.5 (0.5–38.7), Cmax (ng/ml) 18.5 (2.1–74.7), Tmax (h) 1.6 (0.4–8.0), AUC (ng·h/mL) 151.2 (31.2–2525), T1/2 (h) 9.4 (6.0–31.4)	

Reporting group values	baseline characteristics	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	30	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Data are collected at study entry			
Units: years			
median	43.7		
inter-quartile range (Q1-Q3)	34.3 to 59.1	-	
Gender categorical Units: Subjects			
male	15	15	
female	15	15	
not recorded	0	0	
gender Units: Subjects			
male	15	15	
female	15	15	

Subject analysis sets	
Subject analysis set title	transplantation patients
Subject analysis set type	Full analysis
Subject analysis set description:	
10 heart and 20 lung transplantation patients	

Reporting group values	transplantation patients		
Number of subjects	30		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	30		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Data are collected at study entry			
Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
male	15		
female	15		
not recorded			
gender Units: Subjects			
male	15		
female	15		

End points

End points reporting groups

Reporting group title	baseline characteristics
Reporting group description: baseline characteristics	
Reporting group title	end data
Reporting group description: Observation of tacrolimus blood concentrations	
Subject analysis set title	transplantation patients
Subject analysis set type	Full analysis
Subject analysis set description: 10 heart and 20 lung transplantation patients	

Primary: variability of tacrolimus blood concentrations

End point title	variability of tacrolimus blood concentrations
End point description:	
End point type	Primary
End point timeframe: First 6 days after heart and lung transplantation	

End point values	baseline characteristics	end data	transplantation patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	30	30	
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	9.5 (0.5 to 38.7)	9.5 (0.5 to 38.7)	9.5 (0.5 to 38.7)	

Attachments (see zip file)	Table 1.docx

Statistical analyses

Statistical analysis title	Population pharmacokinetic modelling
Statistical analysis description: nonlinear mixed effects modelling software tool NONMEM (version 7.3.0) A two-compartment linear model with first-order oral absorption was used	
Comparison groups	baseline characteristics v end data v transplantation patients
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Mixed models analysis
Parameter estimate	variability %
Point estimate	0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	97.5
Variability estimate	Standard error of the mean

Notes:

[1] - nonlinear mixed effects modelling software tool NONMEM (version 7.3.0) A two-compartment linear model with first-order oral absorption The modelling process was performed using the stochastic approximation expectation maximisation (SAEM) estimation method with interaction. The likelihood was subsequently established using the Monte Carlo importance sampling EM assisted by mode a posteriori (IMPMAP) estimation method. Parameter precision was estimated using the SIR (sampling importance res

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Once per 6 months	
Adverse event reporting additional description: No adverse events were reported because of insertion of an arterial line or blood sampling from an arterial line	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	transplantation patients
Reporting group description: all patients treated with tacrolimus	

Serious adverse events	transplantation patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (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 %

Non-serious adverse events	transplantation patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)		
Blood and lymphatic system disorders			
anemia	Additional description: Hb <6 mmol/L		
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Endocrine disorders			
Electrolyte imbalance	Additional description: hypophosphatemia, hypomagnesemia, hypokalemia, hypernatremia		
subjects affected / exposed	16 / 30 (53.33%)		
occurrences (all)	16		
Hypoproteinaemia	Additional description: Albumin < 30 g/L		

subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2012	The study changed from single center to multi center for optimizing inclusion of patients

Notes:

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 study violations or deviations are made. All patients fulfilled the entry criteria. Yet, results are analyzed and cannot be shown.

Notes: