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

SPARTACUS

Study report

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1. TITLE PAGE

Study title:

A Multi Center, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Days after Transplantation (Spartacus)

Name of investigational product: tacrolimus

Indication: A pharmacokinetic study of tacrolimus in heart and lung transplantation patients during the first days after transplantation

Brief description:

- Design: prospective, follow-up (observational), open-label, multiple doses study
- Duration follow-up: between day 1 and day 6 post transplantation, and at 1, 3 and 6 months post transplantation
- Dose: therapeutic dose
- Patient population: heart and lung transplantation patients admitted to the Intensive Care department

Name of the sponsor:

Dutch Poisons Information Center

Division of Anesthesiology, Intensive Care and Emergency Medicine

University Medical Center Utrecht

The Netherlands

Protocol identification: This is a phase IV observational and investigator driven study

Study initiation date: on 07/05/2013, the first Informed Consent was signed and on 12/06/2013, the first patient was enrolled the study.

Study completion date: 14/09/2015

Name and affiliation of principal investigator:

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The study was conducted in compliance with the 2008 Declaration of Helsinki and Good Clinical Practice guidelines and the Medical Research Involving Human Subjects Act (WMO), including the archiving of the essential documents. The accredited review board for human studies of the University Medical Center Utrecht (UMCU) approved the study (IRB protocol number 12-200/G-D).

Date of the report:

24th November 2016

2. SYNOPSIS

Study Code: NL40432.041.12
Local IBR Code: 12-200

Title: A Multi Center, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Days after Transplantation (Spartacus)

Location of study: This study was performed at the Intensive Care of the University Medical Center of Utrecht in collaboration with the Antonius Hospital of Nieuwegein, The Netherlands. This study is a collaboration between doctors of the Dutch Poisons Information Center, department of intensive care, heart and lung transplantation departments, and the department of pharmacology.

Sponsor: Dutch Poisons Information Center
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Publication (reference): Not applicable

Studied period: June 2013 – September 2015

Name of product: Tacrolimus, prograft®, productcode 301601

Clinical phase: IV, observational study

Study population:
Each heart and lung transplantation patient fulfilling all of the inclusion criteria and none of the exclusion criteria, listed below, 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. Lung transplantation patients are patients with and without cystic fibrosis. These transplantations are performed with or without extracorporeal circulation. Heart transplantation will always be performed with extracorporeal circulation.

Inclusion criteria
- Patients ≥ 18 years
- Patients admitted to the Intensive Care of the UMC Utrecht after heart or lung transplantation
- Treated with tacrolimus (Prograft®; Astellas Pharma Europe)
- Informed consent obtained

Exclusion criteria
- Patients < 18 years
- Patients who die within one day after admission to the ICC of UMCU
- Withdrawal of informed consent
- Allergy towards tacrolimus or macrolides
- Patients on total parenteral nutrition

Primary objective:
To show that the variability of whole-blood and unbound plasma tacrolimus concentrations during the first 6 days post-transplantation is larger than the variation of tacrolimus concentrations in a stable clinical situation.

Secondary objectives:
- To show that unbound tacrolimus plasma concentrations can better predict the occurrence of kidney dysfunction than whole-blood tacrolimus concentrations.
- Identification of variables influencing the unbound tacrolimus plasma concentrations.
- To evaluate whether variations in tacrolimus concentrations in the first days after lung transplantation in cystic fibrosis patients are higher than in patients without cystic fibrosis.

Long-term objective:
- The data will be used to develop a kinetic model in order to dose tacrolimus more accurately to prevent adverse effects of tacrolimus.

Procedures
We performed a multiple doses, open-label, observational, prospective and multi-center study in heart and lung transplant recipients. Informed consent was obtained at the outpatient's department before the transplantation. Only transplanted patients treated with

tacrolimus were included. Presence or absence of cystic fibrosis was recorded among lung transplant recipients. Observations were carried out at the intensive care, during the first 6 days after transplantation. Tacrolimus is administered orally twice daily, according to the usual procedure of the intensive care. Blood and urine was collected. Concomitant drugs as a cause of kidney dysfunction were recorded and plasma concentrations of nephrotoxic drugs were measured at supposed steady state. Renal function is also evaluated in a later phase in de outpatient department after circa 1, 3 and 6 months.

Methods:
Blood concentrations of tacrolimus were measured (whole-blood and unbound concentrations). Individual whole-blood and unbound concentrations-time curves are derived over the 6 days (or less if the patient was discharged earlier from the intensive care unit). Population pharmacokinetic modelling of tacrolimus (whole-blood and unbound concentrations) will be performed, using NONMEM and R. The absorption, the apparent clearance, and the apparent volume of distribution, will be determined as well as the related inter-individual and inter-occasional variability of these structural model parameters. Further, covariate analyses will be performed to establish the relationships between the kinetic parameters and covariates (i.e., patient specific variables) to explain the parameter variability. The following covariates are studied: plasma proteins (albumin, α1-acid glycoprotein (AGP), and high density lipoprotein (HDL)), erythrocytes concentration in blood (erythrocytes and hematocrit), pH, genotyping of CYP 3A4/ 3A5 and P-glycoprotein, gut motility (ileus or diarrhea), and liver function. In addition, we will investigate the relationship between whole-blood tacrolimus concentrations and the unbound tacrolimus plasma concentrations and kidney function during the first 6 days post transplantation. Kidney function is observed for 6 months.

Number of patients: Thirty transplantation patients are studied. Ten heart transplant recipients and 20 lung transplant recipients, of which 10 cystic fibrosis patients, are analyzed as planned. Single lung transplantation is performed in two patients and double lung transplantation is performed in 18 patients. During the observation period, nine patients were treated with ECMO (Extracorporeal Membrane Oxygenation). The diagnosis for lung transplantation is cystic fibrosis, interstitial lung disease, chronic obstructive pulmonary disease and the diagnosis for heart transplantation is ischemic and non-ischemic heart failure, such as giant cell myocarditis, viral myocarditis and hereditary dilating cardiomyopathy.

Test product, dose and mode of administration:
Tacrolimus (Prograft®) is given orally. The initial dose is 0.1 mg/kg bid for lung transplants and 2 mg twice daily for heart transplants. These are the current route and dose of tacrolimus administration at the Intensive Care Department of the UMCU. Adjustment is necessary to achieve a whole-blood tacrolimus trough concentration of 9 -15 ng/mL (daily practice). The tacrolimus dose is adjusted by the attending transplantation physician according to the whole-blood tacrolimus trough concentration measured at 6 am. The result of the extra tacrolimus analyses are not communicated to the physicians in order not to interfere with normal daily practice. This study is an observational study and not an intervention study.

Duration of the treatment: Tacrolimus is standard of care nowadays. Heart and lung transplantation patients need immunosuppressive therapy for the rest of their life. Therefore, tacrolimus treatment is a life-long treatment.

Results: At this moment the database is under construction and will be completed as soon as possible. No analyses have been performed so far. The expected duration for all analyses to be completed is approximately 2 years and therefore we expect to provide a complete report

in March 2019.

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABR	ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee "(ABR = Algemene Beoordeling en Registratie)"
ADQI	Acute Dialysis Quality Initiative workgroup
AE	Adverse Event
AGP	α1-Acid glycoprotein
Alb	Albumin
AR	Adverse Reaction
AUC	Area under the curve
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
Ccr	Creatinine clearance
CF	Cystic Fibrosis

CRF	Case report form
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CL	Apparent clearance of a substance from plasma
CLR	Renal clearance
Cmax	Maximal concentration
CV	Curriculum Vitae
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
EDTA	Ethylenediamine tetra-acetic acid
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
FiO2	Fraction of inspired oxygen in a gas mixture
FKBP	FK506 (=tacrolimus) binding protein
HDL	High density lipoproteins
Hr	Hour
HPLC-MS/MS	High Pressure Liquid Chromatography tandem mass spectrometry
Ht	Hematocrit
IB	Investigator's Brochure
IC	Informed Consent
ICC	Intensive Care Center
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Kg	Kilogram
LUMC	University Medical Center of Leiden
METC	Medical research ethics committee (MREC); in Dutch: "medisch ethische toetsing commissie" (METC)
Ml	Milliliter
NVIC	National Poisons Information Center
NF-AT	Nuclear factor of activated T-cells
PC	Pressure controlled ventilation
Pcr	Plasma creatinine
PEEP	Positive end expiratory pressure
Pg	Page

Pgp	P-glycoprotein
PS	Pressure supported ventilation
(S)AE	(Serious) Adverse Event
SIRS	Systemic inflammatory response syndrome
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
T 1/2	Apparent elimination halve-life
Tmax	Time to reach maximal concentration
Tv	Tidal volume
Ucr	Urine creatinine
UMC	University Medical Center
V	Volume
Vd	Apparent volume of distribution
Wbp	Personal Data Protection Act (in Dutch: "Wet Bescherming Persoonsgevens")
WMO	Medical Research Involving Human Subjects Act (in Dutch: "Wet Medisch-wetenschappelijk Onderzoek met Mensen")

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The accredited review board for human studies of the University Medical Center Utrecht (UMC Utrecht, The Netherlands) approved the study (IRB protocol number 12-200). The study was conducted in compliance with local and national regulatory requirements and laws, including the archiving of the essential documents.

5.2 Ethical Conduct of the Study

The study was conducted in compliance with the 2008 Declaration of Helsinki and Good Clinical Practice guidelines. The Dutch trial registration (NTR) number is 3912 and Eudract study code is NL40432.041.12.

5.3 Patient Information and Consent

All heart and lung transplantation patients are asked prior to surgery to participate in the study by the study nurse or one of the investigators. If they were interested in study participation, they received written information on the study. The patient is offered at least 24 hours to read the information and sufficient opportunity to ask the study nurse or one of the investigators any question. The patient is verbally informed about the study proposal, schedule and (dis-)advantages. The patient does not enter the study if he/she did not

understand the written and verbal information provided and/or if there was no signed and dated consent form. A copy of the written and signed informed consent is provided to the participant, whereas the original version is retained by the investigator. No patient has objected during the study, therefore no patient is withdrawn from the study.

Representative written information for the patient (if any) and a sample patient consent form is provided in appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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7. INTRODUCTION

Tacrolimus is used as prophylaxis for organ rejection in lung, heart, liver and kidney transplantation. Although knowledge about tacrolimus pharmacokinetics is extensive, it remains difficult to dose tacrolimus correctly. High inter- and intra-individual variability in tacrolimus blood concentrations has been observed among transplant recipients. Sub-therapeutic blood concentrations of tacrolimus may result in organ rejection, whereas supra-therapeutic blood concentrations may be toxic and result in organ (renal) dysfunction. Correct dosing of tacrolimus is of prognostic importance, especially in r heart and lung transplantation patients in the first days after transplantation.

A specific difficulty is that pharmacokinetics of drugs in heart and lung transplanted patients in the days directly after transplantation differ from pharmacokinetics some weeks or years after transplantation, when the clinical situation of patients has stabilized. For instance, in these days, transplanted patients may present a Systemic Inflammatory Response Syndrome (SIRS) or shock, especially after a long runtime of extracorporeal circulation. SIRS and shock may cause hemodynamic instability with multiple organ dysfunction and failure or altered protein metabolism, acid-base imbalance, electrolyte disturbances, activation of coagulation, fluid overload, and diminished hematopoiesis. Most of these alterations may influence pharmacokinetics of tacrolimus separately. In practice, during the days directly after transplantation, the tacrolimus dose is adjusted daily at 6 pm, based on whole-blood tacrolimus concentrations measured at 6 am. Adjustment of tacrolimus dosing does not take into account the possible pharmacokinetic changes that might have occurred since the measurement.

Most research on pharmacokinetics of tacrolimus in transplant recipients has been performed in renal and liver transplant recipients and mostly after a month up to a few years after transplantation. However, few studies have focused on heart and lung transplant recipients, the pharmacokinetics of tacrolimus in heart or lung recipients directly after transplantation have not been fully elucidated[1,2,3]. For instance the unbound tacrolimus plasma concentrations might explain toxicity of tacrolimus better than the whole-blood tacrolimus concentrations. Unbound tacrolimus plasma concentrations have never been taken into account in these patients. Knowledge about the variables influencing the unbound tacrolimus plasma concentrations in a relevant way may help to identify the patient at risk for inadequate tacrolimus dosing. Inadequate dosing increases the chance for adverse effects. This study identifies the patient at risk for inadequate tacrolimus dosing.

Changes in absorption, distribution, metabolism and clearance can influence the inter- and intra-individual variability in tacrolimus concentrations[4]. We carried out an observational study on the pharmacokinetics of tacrolimus whole-blood and unbound plasma concentrations in heart and lung (CF and non-CF) transplant recipients in the first days after transplantation with a follow up period of approximately 6 months to monitor kidney dysfunction. With the results of this study, insight in pharmacokinetics of tacrolimus directly after transplantation will be improved. This knowledge improves the dosage of

tacrolimus, which optimizes patient's safety.

This study is an investigator driven and observational study. No interventions have been done. The local valid guidelines of heart and lung transplantation, which are in accordance with international guidelines, are used for the treatment of the patients.

The primary objective is to show that the variability of whole-blood and unbound plasma tacrolimus concentrations during the first 6 days post-transplantation is larger than the variation of tacrolimus concentrations in the stable clinical situation.

Due to its completeness, this study will be of substantial value for transplantation patients. With the novel knowledge developed with this study we expect to be able to improve the tailoring of tacrolimus dosing in heart and lung transplantation patients. The result will be a decrease in side and toxic effects, and thus an increase in patient's safety.

8. STUDY OBJECTIVES

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

Secondary objectives:

- To show that unbound tacrolimus plasma concentrations can better predict the occurrence of kidney dysfunction than whole-blood tacrolimus concentrations.
- Identification of variables influencing the unbound tacrolimus plasma concentrations.
- To evaluate whether variations in tacrolimus concentrations in the first days after lung transplantation in cystic fibrosis patients are higher than in patients without cystic fibrosis.

Long-term objective:

- The data will be used to develop a kinetic model in order to dose tacrolimus more accurately to prevent adverse effects of tacrolimus.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

We perform a prospective, single center, observational, open label study with tacrolimus in heart and lung transplant recipients admitted to the Intensive Care of the University Medical Center Utrecht. Due to the observational design of the study, neither blinding, nor randomizing, nor matching is done.

Twelve hour pharmacokinetic profiles of whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations are obtained. Pharmacokinetic parameters are observed in 10 heart and 20 lung transplant recipients up to the first 6 days after transplantation or shorter if patients are discharged from the intensive care earlier. Renal function is evaluated in the first 6 days and 1, 3 and 6 months after transplantation in the out-patient department. No data safety monitoring board is used in this observational study.

Before transplantation:
After signing the informed consent form, and before the transplantation, the following procedures are applied:

- Collection of demographic data (age, gender, weight, length, and attribution of a Unique Trial Number).
- Recording of medical history, indication of transplantation (heart or lung failure, Cystic Fibrosis or not), and presence of pre-transplant renal dysfunction.

After transplantation:
Directly after transplantation and after arrival at the Intensive Care, the following procedures are applied:

- Day 1 was defined as the day of admission to the intensive care, day 2 to day 6 were defined as the days following the admission to the intensive care. Discharge could take place either on day 2, 3, 4, 5 or 6. In case of discharge before day 6 the observation stopped for the first period.
- Clock time at which first tacrolimus administration started is recorded in the CRF. Every day at 6 am and 6 pm tacrolimus is administered. Dosing is done by the transplantation physicians according to daily practice; starting with 0.1 mg/kg/day bid, thereafter based on whole-blood tacrolimus concentrations of 6 am. Whole-blood tacrolimus concentrations of 6 am are shown to the attending physicians. All other measurements of tacrolimus are not revealed to the caretakers.
- Whole-blood tacrolimus concentrations will be measured prior to dosage (t=0 hours; baseline) and at t = 1, 1 ½, 2, 2 ½, 3, 4, 6, 8, and 12 hours after each tacrolimus administration at 6 pm for a maximum of 6 days until discharge of the Intensive Care Unit. The unbound tacrolimus plasma concentrations are measured at 0, 2 and 6 hours after each tacrolimus dose at 6 pm for non-CF patients and at 0, 3 and 6 hours after each tacrolimus dose at 6 pm for CF patients. Every day at 6 pm the following blood samples are drawn for measurements of biochemical, hematological and other parameters: kidney function (urea, creatinine) and liver function (bilirubin, ALAT), HDL, albumin, alpha1-acid-glycoprotein. When patients are discharged to the ward before day 6 routinely measured urea and creatinine are recorded in the CRF. Whole-blood tacrolimus concentrations at 6 am (the so-called whole-blood tacrolimus 'trough' concentrations) will be analyzed every day. The remaining whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations are analyzed afterwards in a batch and are not available to the treating physician.
- Blood is drawn from an arterial line catheter, which is already inserted in every patient in current daily practice.
- All mentioned study parameters are recorded in the CRF. The following parameters are also recorded in the CRF: 24 hours urine output, temperature, heart frequency, respiratory rate, setting parameters of mechanical ventilation (Pressure control/Pressure support, inspiratory plateau pressure/PEEP, FiO2, tidal volume). The routine parameters are performed according to standard analyses.
- The following blood collecting tubes are used: Li-heparin gel (light green) 3 mL, EDTA (pink) 1 mL, EDTA (pink) 2 mL, EDTA (purple) 3 mL, EDTA (purple) 5 mL, 0.5 ml Sarstedt cryovials (for α-1-acid glycoprotein 1 mL). Each blood sample is given a barcode with the Unique Trial Number. All samples 0 – 64 and month 1,3 and 6 per unique trial number are collected and send to the laboratory as soon as possible (otherwise stored at -80 °C until transport). Samples for measurement of α-1-acid glycoprotein per unique trial number are immediately centrifuged (1500 g) and plasma, prepared from these samples, is stored in 0.5 mL vials (Eppendorf vials) at -80 °C until assay measurement.
- To measure 24 h creatinine clearance in every patient, urine is collected 24 hours a day for a maximum of 6 days or less until discharge from the intensive care unit. A urine catheter is already introduced in every patient for routine care. Urine collectors are stored and analyzed by the clinical chemical laboratory of the UMCU.
- Plasma concentrations of (val)acyclovir, (val)ganciclovir, tobramycin, if administered, are measured at steady state on day 3 and 6, just before and 3 hours after administration

and plasma concentrations of sulfamethoxazole are measured on day 3 at steady state before administration.

- SOFA score (sequential organ failure assessment score), which is a severity of disease classification system, is recorded on the intensive care once a day.
- After circa 1, 3 and 6 months at the out-patient department :
  Plasma creatinine is measured and recorded in the CRF for each patient after circa 1, 3 and 6 months. Urine is collected for 24 hours to calculate creatinine clearance. Whole-blood tacrolimus trough concentration is recorded in the CRF. In case of kidney dysfunction, plasma concentrations of concomitant drugs (e.g. sulfamethoxazole, valganciclovir, intravenous colistine, azitromycin, amfoB) are analyzed.

9.2 Discussion of Study Design, including the Choice of Control Groups

This study is performed to increase knowledge about tacrolimus pharmacokinetics in relation to toxicity. This is not an efficacy study. Therefore, no comparison is needed, nor blinding of the treatment. Observations of daily practice are performed and no interventions are done. Tacrolimus is administered twice daily as is practice in heart and lung transplantations nowadays.

Patient's safety will increase due to a better insight in tacrolimus pharmacokinetics early after transplantation. No supplementary pain is suffered by introducing an arterial line or a urinary catheter. All patients are already equipped with an arterial line to draw blood samples, corresponding to current daily practice. The maximum amount of blood removed per patient is circa 50 ml per day or a maximum of 300 ml for 6 days (a minimum of 15 ml per day or 90 ml for 6 days is common after heart and lung transplantations) and an additional 2,5 ml after circa 1, 3 and 6 months. Concerning the urine collection, on the intensive care all patients are equipped with a urine catheter to current daily practice. Additionally, at 1,3 and 6 months urine is collected for 24 hours by the patient and one blood sample is drawn via venal puncture as standard care.

9.3 Selection of Study Population

9.3.1 Inclusion criteria

- Patients $\geq$ 18 years
- Patients admitted to the Intensive Care of the UMC Utrecht after heart or lung transplantation
- Treated with tacrolimus (Prograft®; Astellas Pharma Europe)
- Informed consent obtained

9.3.2 Exclusion criteria

- Patients < 18 years
- Patients who die within one day after admission to the ICC of UMCU
- Withdrawal of informed consent
- Allergy towards tacrolimus or macrolides
- Patients on total parenteral nutrition

When patients die within one day pharmacokinetic profiles cannot be performed properly, which hampers the interpretation of the profiles. Therefore, these patients are excluded. Parenteral nutrition may influence the tacrolimus blood concentrations in any direction, decreasing as well as increasing blood concentrations, which makes it very difficult to interpret the tacrolimus blood concentrations. Therefore intravenous nutrition is an

exclusion criterion.

9.3.3 Removal of patients from therapy or assessment

No patients were withdrawn from the study during the first 6 days on the intensive care. One patient was lost in the follow up period after one month, because tacrolimus was stopped.

9.4 Treatments

9.4.1 Treatments administered

Every day at 6 am and 6 pm tacrolimus is administered. Dosing is done by the attending physicians according to daily practice; starting with 0.1 mg/kg/day bid for the lung transplantation patients and 2 mg bid for the heart transplantation patients. Hereafter, dosing is based on whole-blood tacrolimus concentrations of 6 am. Whole-blood tacrolimus concentrations of 6 am are shown to the attending physician. All other measurements of tacrolimus are not revealed to the caretakers.

9.4.2 Identity of investigational product(s)

Tacrolimus, prograft®, with product code 301601, ATC group L04 A05 and marketing authorization holder Astellas Pharma Europe, is distributed by the Pharmacy of the UMC Utrecht to the intensive care. The stability of tacrolimus is established by Astellas Pharma Europe. The accurate storage and transport of tacrolimus is guaranteed by the Pharmacy of the UMCU, which is CCKL and ISO accredited.

A hard capsule of 0.5 or 1 mg is used for dosing. No placebo or comparator product is used.

9.4.3 Method of assigning patients to treatment groups

No randomization is performed.

9.4.4 Selection of doses in the study

The initial dose is 0.1 mg/kg/day bid for the lung transplantation patients and 2 mg bid for the heart transplantation patients. Further dosing is based on whole-blood tacrolimus trough concentrations of 6 am.

9.4.5 Selection and timing of dose for each patient

Timing is twice daily, 6 am and 6 pm, as per transplantation protocol in heart and lung transplant patients. There is no fixed dose. The dose is based on whole-blood tacrolimus concentrations at 6 am. The therapeutic range is from 9 to 15 ng/ml as target concentration. The dosing is further based on variations in gut motility, renal or liver dysfunction, and concomitant drugs increasing or decreasing tacrolimus concentrations. No restrictions for feeding or timing of feeding have been made in the study protocol because of the observational character of the study. Transplantation patients who are mechanically ventilated or have gut dysmotility are fed by continuous enteral nutrition via a nasogastric tube. Clinical stable patients, which are not mechanically ventilated, were aloud to eat normal meals.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and concomitant therapy

All concomitant drugs are recorded. Drug-drug interactions with tacrolimus are analyzed. Drugs often administered to transplantation patients and influencing renal function are recorded and blood concentrations are analyzed. Plasma concentrations of (val)acyclovir, (val)ganciclovir, tobramycin, if administered, are measured at steady state on day 3 and 6 just before and 3 hours after administration and plasma concentrations of sulfamethoxazole are measured on day 3 at steady state before administration.

9.4.8 Treatment compliance

Compliance is secured. Tacrolimus is administered at the intensive care by the nurses, which is daily practice. The timing of tacrolimus administration is recorded in the CRF.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and safety measurements assessed and flow chart

All patients were equipped with an arterial catheter inserted by intensive care doctors. Adverse events by introducing an arterial catheter for blood sampling and for continuous blood pressure measurement, are recorded, which are for instance infections or hemorrhage from the arterial catheter (> 200 ml per day). Because an arterial line is already inserted and low risk is expected in this observational study, they are reported once per 6 months. Sampling is performed by two researchers and a study nurse, trained for sampling via an arterial line. All SUSARs are reported through the web portal ToetsingOnline to the accredited METC that approved the protocol.

Adverse events (AEs) will be registered in the CRF throughout the study period. To

facilitate summarizing of AEs, reported AE terms are coded to a standard set of 'preferred terms' as defined in the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence and the incidence of possible or probable tacrolimus-related events aresummarized (including statements on the severity of events). An adverse event that occurs during the observation period (6 days after transplantation) or at follow-up (up to 6 month after transplantation) is only counted as an adverse event if it was either not present at baseline or it was present at baseline but increases in severity during the treatment period.

Serious adverse events like; death, prolongation of existing inpatients' hospitalization or requiring hospitalization, repeated surgery, significant disability or incapacity, wound complications, serious bleeding (> 1000 ml per day), sepsis, multi organ failure, prolonged mechanical ventilation (>1 day), arrhythmias, pericardial tamponade, severe anemia, disseminated intravascular coagulation, severe electrolyte disturbances, disturbances of proteins, bowel disturbances, weight loss, decubitus, encephalopathy or delirium, pericardial or pleural effusion and pain, are often seen in heart and lung transplantation patients and not due to blood sampling via an arterial catheter. Due to the observational nature of the study, these events are not due to this study and therefore they are not reported separately. They are recorded in the CRF.

All adverse events are followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Serious adverse events if not mentioned before are reported to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse event. All SUSARs are reported through the web portal ToetsingOnline to the accredited METC.

9.5.2 Appropriateness of measurements

The immunosuppressant tacrolimus has been of paramount importance in the modern era of heart and lung transplantation since the nineties. Tacrolimus acts as a potent calcineurin inhibitor and has significantly contributed to contemporary 5-year-survival rates of roughly 85%[5]. In most studies, tacrolimus exhibits higher patient and organ survival rates than the calcineurin inhibitor cyclosporine. Moreover, tacrolimus leads to lower rejection rates and longer freedom of rejection[6-8]. Another alternative for tacrolimus is sirolimus, an mTOR inhibitor, which has the same 5-year-survival rates, although tacrolimus has been reported to have a higher freedom from rejection rate after 5 years (82% vs 73%). Sirolimus is also poorly tolerated and more than half of the patients discontinue its use[5]. At present, prioritizing efficacy, tacrolimus is the first choice immunosuppressive drug for heart and lung transplant recipients. Consequently, improving tacrolimus treatment in heart and lung transplant recipients is of utmost importance.

9.5.3 Primary efficacy variable(s)

This study is not an efficacy study, therefore not applicable.

9.5.4 Drug concentration measurements

(See also schedule below) Whole-blood tacrolimus concentrations are measured prior to dosage (t=0 hours; baseline) and at t = 1, 1 ½, 2, 2 ½, 3, 4, 6, 8, and 12 hours after each tacrolimus administration at 6 pm for a maximum of 6 days until discharge of the Intensive Care Unit. The unbound tacrolimus plasma concentrations are measured at 0, 2 and 6 hours after each tacrolimus dose at 6 pm for non-CF patients and at 0, 3 and 6 hours after each tacrolimus dose at 6 pm for CF patients.

Tacrolimus whole-blood concentrations are measured as shown in the schedule. A 12 hour curve from 6 pm up to 6 am is sampled as per transplantation protocol in heart and lung transplants. The dose is based on whole-blood tacrolimus concentrations at 6 am. The therapeutic range is 9 to 15 ng/ml as target concentration. Dosing is further based on variations in gut motility, renal or liver function, and concomitant drugs increasing or decreasing tacrolimus concentrations. No restrictions for feeding or timing of feeding have been made in the study protocol because of the observational character of the study. Transplantation patients who are mechanically ventilated or have gut dysmotility are fed by continuous enteral nutrition via a nasogastric tube. Clinical stable patients are aloud to eat meals

Plasma concentrations of (val)acyclovir, (val)ganciclovir, tobramycin, if administered, are measured at steady state on day 3 and 6 before and 3 hours after administration and plasma concentrations of sulfamethoxazole are measured on day 3 at steady state before administration.

Table 1. Schedule of blood sampling and tacrolimus administration

actual time	Day 1 6:00 AM	Day 1 6:00PM	6:05 PM							Day 2 12:00 AM		6:00 AM	6:05 AM
scheme time	-12	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	0	1		2	3	4	5	6	7	8	9	10	
administration of tacrolimus	x		x										x
tacrolimus whole blood	o	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction		x/ x CF				x		x CF		x/ x CF			
biochemical/haematological		x											
pH		x											
AGP		x											
serum		x											
Cyp3A4/cyp3A5/Pgp		x											
Ganciclovir/Acyclovir/Tobramycin													
Sulfamethoxazole													

o: 1ml of blood is withdrawn for baseline measurement if the patient starts with tacrolimus at 6 AM

actual time	Day 2 6:00 PM	6:05 PM							Day 3 12:00 AM		6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	11		12	13	14	15	16	17	18	19	20	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 3 8:00 AM		11:00 AM
scheme time	14		17
vial number	21		22
administration of tacrolimus			
tacrolimus whole blood			
tacrolimus unbound fraction			
biochemical/haematological			
pH			
AGP			
serum			
Cyp3A4/cyp3A5/Pgp			
Ganciclovir/Acyclovir/Tobramycin	x		x
Sulfamethoxazole	x		

actual time	Day 3 6:00 PM	6:05 PM	1	1,5	2	2,5	3	4	Day 4 12:00 AM	8	6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	23		24	25	26	27	28	29	30	31	32	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 4 6:00 PM	6:05 PM	1	1,5	2	2,5	3	4	Day 5 12:00 AM	8	6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	33		34	35	36	37	38	39	40	41	42	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 5 5:55 PM	6:00 PM	1	1,5	2	2,5	3	4	Day 6 12:00 AM	8	6:00 AM	6:05 AM
scheme time		0	1	1,5	2	2,5	3	4	6	8	12	
vial number		43	44	45	46	47	48	49	50	51	52	
administration of tacrolimus	x											x
tacrolimus whole blood		x	x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction		x/ x CF			x		x CF		x/ x CF			
biochemical/haematological		x										
pH		x										
AGP		x										
serum		x										
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 6 8:00 AM		11:00 AM
scheme time	14		17
vial number	53		54
administration of tacrolimus			
tacrolimus whole blood			
tacrolimus unbound fraction			
biochemical/haematological			
pH			
AGP			
serum			
Cyp3A4/cyp3A5/Pgp			
Ganciclovir/Acyclovir/Tobramycin	x		x
Sulfamethoxazole	x		

actual time	Day 6 6:00 PM	6:05 PM							Day 7 12:00 AM		6:00 AM	Day 7 6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	55		56	57	58	59	60	61	62	63	64	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

xCF in cystic fibrosis patient samples wil be withdrawn one hour after patients without Cystic fibrosis

	month 1
administration of tacrolimus	x
whole-blood tacrolimus	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

	month 3
administration of tacrolimus	x
whole-blood tacrolimus	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

	month 6
administration of tacrolimus	x
whole-blood tacrolimus	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

9.6 Data Quality Assurance

Handling and storage of blood and urine samples:
Clinical laboratory and tacrolimus samples collected during this study are analyzed by the clinical chemical and pharmaceutical laboratory of the UMCU (Utrecht, The Netherlands). Samples for measurement of unbound tacrolimus plasma concentrations are stored at -80°C and are analyzed afterwards at thepharmacological laboratory of UMCU. Serum samples for AGP measurement are stored at -20°C and analyzed by the laboratory of University Medical Center of Leiden (LUMC). Samples Cyp3A4/Cyp3A5/Pgp are analyzed by the laboratory of the Department Clinical Chemistry (AKC) of the Erasmus Medical Center, Rotterdam. The Investigator maintains on file, written evidence that these facilities are certified/accredited under applicable regulations. Residual plasma samples will be stored at -80 °C and will possibly be used at later time points (within 5 years).

Liquid Chromatography–Tandem Mass Spectrometry Instrumentation (LC MS/MS) a liquid chromatography system comprising of auto sampler and micro pumps (Thermo Fisher Scientific) are used for tacrolimus quantification. The lower limit of quantification (LOQ) for tacrolimus is 0.5 µg/L. The interday variability of the tacrolimus measurements is <5%, secured by the pharmaceutical laboratory UMCU. Clinical laboratory assays are performed according to standardized procedures. All assays are validated according to the guidelines set by CCKL.

Measurement of unbound tacrolimus plasma concentrations is developed in the clinical pharmacy laboratory of Utrecht. The sample preparation for the determination of the

unbound tacrolimus plasma concentrations consists of an easy-to-use ultrafiltration step followed by solid phase extraction. To determine the total concentration of tacrolimus in plasma a simple protein precipitation based method is developed. Extracts are injected on a Thermo Scientific HyPurity C18 column using a gradient elution. The analytes are detected by liquid chromatography-mass spectrometry using a triple quadrupole with positive ionization.

Handling and storage of data and documents:
After informed consent for participation, each participant is given a Unique Trial Number. Subjects are only traceable by this number to the clinical investigators. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

Data are encoded by the Unique Trial Number. All data are recorded in the CRF. All missing data are explained. CRF items not done are marked as "ND". If an item is unknown or not applicable to the specified case, the space on the CRF is marked "NA". Data that has been collected but cannot be retrieved are also marked "NA". All data entries are made in permanent, black ink. Entry errors do have a single line drawn through them with the correction entered above. All entry errors are initialed and dated. The Investigator of this study is responsible according to ICH-GCP guidelines for assuring proper study conduct with regard to protocol adherence and validity of the data recorded on the CRFs.

The investigator has therefore assigned a qualified study monitor to this study (see also 16.1.4 Monitoring plan). The monitor assists the investigators in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitor ensures that the investigator understands all applicable regulations concerning the clinical evaluation of an investigational drug, as laid down in ICH GCP guidelines. The investigator has allowed the monitor direct access to the study drug dispensing and storage area and to all clinical data of the study subjects for the above purposes and assisted the monitor in these activities. The monitor has visited the center at regular intervals, once per 3 months, to review and verify the data collected. The monitor has regarded all information that is supplied to him as strictly confidential. Further information on monitoring the data can be found in the monitoring plan which is added to this study protocol (See 16.1.4).

Data are entered into a database. All data are entered by means of double entry verification. Queries are issued, e.g. on missing data, inconsistencies, illegible data, illegal values and unclear corrected items. Clinical research personnel assigned by the Principal Investigator has required direct access to the subject's notes for source data verification. The confidentiality of all the subjects' identities are maintained. Only the Unique Trial Number is used on CRFs and in all study correspondence. No material bearing a subject's name is kept on file by the clinical research personnel.

The principal investigator maintains a study file, which is used to file the protocol, correspondence with the independent ethics committee (IEC) and other study-related documents. The principal investigator's copy of the case report forms (CRF), study file, consent forms, and the subject identification list are kept by the investigator for at least 20 years.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans

Concentration over time curves

The following concentration-time curves are derived for each patient for the 6 days (or less if the patient is discharged earlier from the intensive care unit):

- 12-Hour whole-blood total tacrolimus concentrations.
- 12-Hour unbound tacrolimus plasma concentrations.

The variance in whole-blood tacrolimus trough concentrations of stable patients is known from the literature (8.4 µg/L with a standard deviation (SD) of 2.1 at 6 months post-transplantation *25*. An F test will be used to compare the variance in our study (sigma 1 squared) with the variance found in the literature for stable patients (sigma 2 squared). We expect the SD of tacrolimus trough concentration in whole-blood at day 4 to be at least 5 times larger than at 6 month post-transplantation (so at least a SD>10, estimation based on own unpublished data, at day 4: mean tacrolimus concentration of 18.3 µg/L with a SD of 12.3 µg/L). The F test will be used to compare the two variances: the variance in the present study ($\sigma 1$) squared with the variance found in the literature ($\sigma 2$) squared. The null hypothesis is that both variances are equal. The alternative hypothesis is that $\sigma 1$ is larger than $\sigma 2$ (upper one-tailed test).

Kinetic parameters for whole-blood tacrolimus concentrations will be calculated: AUC, Cmax, Cmin, Tmax, apparent clearance, apparent volume of distribution..
Pharmacokinetics of tacrolimus will be analyzed by nonlinear mixed-effects modelling (in NONMEM or R). A nonlinear mixed-effects model consists of two sub-models: a structural model (fixed effects) and a stochastic model (random effects). Both the structural and stochastic parameters are simultaneously estimated by fitting the model to the data.

The structural model will describe the relationship between dose and concentration in terms of structural pharmacokinetic parameters (i.e. volume of distribution (Vd), clearance (CL)).

The stochastic model will describe the random variability in the structural model parameters. One kind of random effects is the inter-individual variability (unexplained differences between individuals due to biology, for instance). Inter-individual variability describes the random variability of structural parameters within the population.

Another kind of random effects is the inter-occasion variability in case of repeated measurements. Inter-occasion variability describes the variability of an individual parameter value from one occasion to another.

A second level of stochastic effects describes the variability of the difference between observed and predicted response ($\sigma 2$, variance of the residual error). $\sigma 2$ includes among other factors, model misspecification, intra-individual variability, and measurement error.

Covariate analyses

One of the important aims in population pharmacokinetic modelling is the establishment of relationships between parameters and covariates (i.e. patient specific variables) to explain parameter variability and facilitate dose adjustment decisions.

Descriptive statistics of the following covariates, selected on the basis of their known or theoretical relationships with pharmacokinetics of tacrolimus, will be performed: hematocrit, SIRS, APACHE-score, SOFA-score, pH, albumin, $\alpha 1$-acid glycoprotein, high density lipoprotein, gut dysmotility (diarrhea or ileus), liver and renal functions, continuous renal replacement therapy, fluid balance or body weight, possible drug-drug interaction with concomitant medication, cystic fibrosis, polymorphisms in CYP3A4, CYP3A5 and P-glycoprotein.

The search for important covariates is not straightforward, especially if there are large numbers of covariate-parameter relations to consider. Covariate models will be built for

identifying candidate covariate effects and to test the importance of found covariate terms, according to the so-called "stepwise covariate model building strategy" *26*. The obtained minimum value of the objective function defined as minus twice the log likelihood will be used for model comparisons.

Other statistical analyses

In addition, we will investigate the relationship between tacrolimus whole-blood and unbound plasma concentrations and kidney function during the first 6 days post transplantation.

9.7.2 Determination of sample size

A sample size calculation has been performed showing that the minimum sample size is 5 patients per sample (with a 90% confidence and a 95% power for an estimated $\sigma 1 = 10$ and $\sigma 2 = 2.1$).

The variance in whole-blood tacrolimus trough concentrations of stable patients is known from the literature (8.4 µg/L with a standard deviation (SD) of 2.1 at 6 months post-transplantation[9]. An F test will be used to compare the variance in our study (sigma 1 squared) with the variance found in the literature for stable patients (sigma 2 squared). We expect the SD of tacrolimus trough concentration in whole-blood at day 4 to be minimum 5 times larger than at 6 month post-transplantation (so at least a SD>10, estimation based on own unpublished data, at day 4: mean tacrolimus concentration of 18.3 µg/L with a SD of 12.3 µg/L). The F test will be used to compare the two variances: the variance in the present study ($\sigma 1$) squared with the variance found in the literature ($\sigma 2$) squared. The null hypothesis is that both variances are equal. The alternative hypothesis is that $\sigma 1$ is larger than $\sigma 2$ (upper one-tailed test).

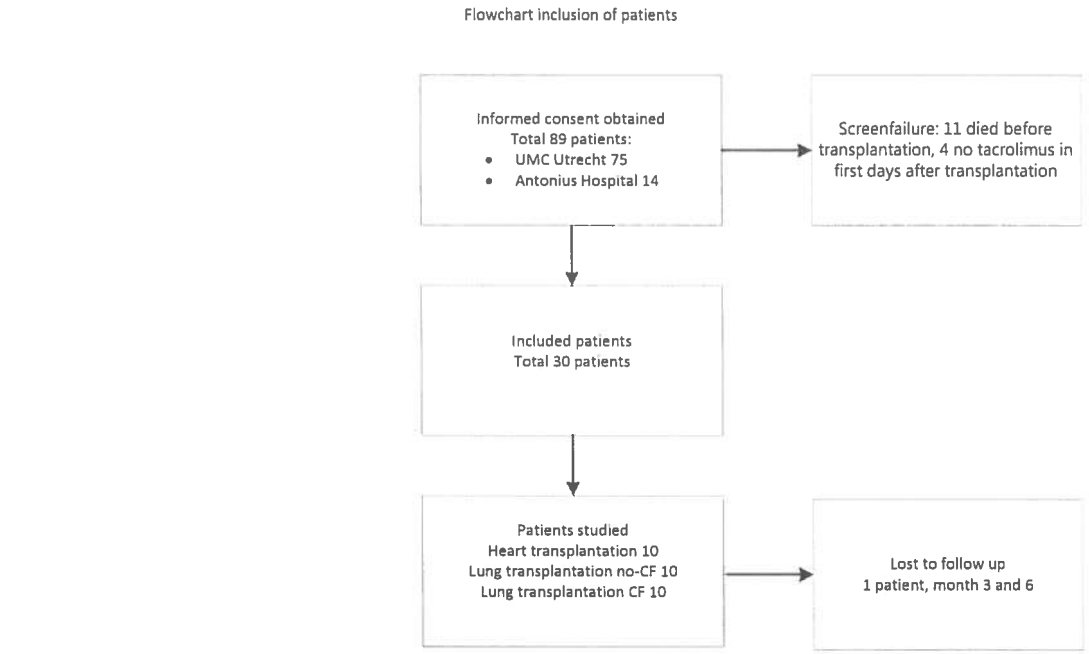
9.8 Changes in the Conduct of the Study or Planned Analyses

There are no changes in the conduct of the study.

10. STUDY PATIENTS

10.1 Disposition of Patients

All patients on the waiting list for heart or lung transplantation in the UMC Utrecht are asked for informed consent after the nature and purpose of the investigation is explained to them in order to get consent of the patients themselves. Only the patients fulfilling the inclusion and not the exclusion criteria, for instance a heart or lung transplantation, are included after they have signed a study specific informed consent form. The amount of informed consents exceeds the amount of included patients. This is anticipated and due to the design of the study.



Number of patients included in time

June 2013	July 2013	August 2013	Sep 2013	Oct 2013	Nov 2013	Dec 2013	Jan 2014	Feb 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	Sep 2014	Oct 2014	Nov 2014	Dec 2014	Jan 2014	Feb 2014
1	2	1	1	1	4	5	1	0	3	2	2	0	0	0	2	1	2	0	1	1

Figure1. Flowchart of disposition of patients

10.2 Protocol Deviations

No study violations or deviations are made. All patients fulfilled the entry criteria.

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

In this study toxicity is observed, no efficacy analysis are performed. All patients completed the study. Patients are observed, no randomization is performed.

11.2 Demographic and Other Baseline Characteristics

Not applicable

11.3 Measurements of Treatment Compliance

Urine is not collected for patient number 6 at 3 and 6 months, number 9, 19 and 21 at month 3. Reasons for these missings are non compliance in urine collection. And for patient 6, the reason is that tacrolimus is stopped.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of efficacy

Not applicable.

11.4.2 Statistical/analytical issues

Not available

11.4.3 Adjustments for Covariates

Not available

11.4.4 Handling of Dropouts or Missing Data

There are no dropouts during the observation period. All possible efforts will be made to fulfill the protocol requirements concerning the collection of data in order to reduce the number of missing data. In the follow up period, urine not collected for one patient at 3 and 6 months. There are missing data for creatinine clearances in 3 patients at month 3, because of non-compliance. Only a few patients are missing a small sample of covariates. In these cases, imputing missing covariate values will be preferred to exclusion, preferably using maximum likelihood procedures for predicting each predictor from all other predictors.

11.4.5 Interim Analyses and Data Monitoring

Not applicable

11.4.6 Multicentre Studies

This is a multicenter study in the sense that two centers have obtained informed consent. The actual study, the observational period in which the pharmacokinetic samples are obtained, is conducted in one center, the University Medical Center Utrecht. Both centers work together as one transplantation center. Therapy is similar in both centers. In addition, two patients from the Antonius Hospital Nieuwegein are included in the study. The number of patients is therefore too low to analyze separately.

11.4.7 Multiple Comparisons/Multiplicity

We will minimize multiplicity as much as possible. If any aspect of multiplicity remains, adjustment to the Type I error will be considered.

11.4.8 Use of an "Efficacy Subset" of Patients

Not applicable

11.4.9 Active-Control Studies Intended to Show Equivalence

Not applicable

11.4.10 Examination of Subgroups

Observations are clustered as heart transplant recipients, lung transplant recipients with CF and without CF. A sample size calculation is done prior to the study showing that the minimum sample size is 5 patients per sample (with a 90% confidence and a 95% power for an estimated $\sigma 1 = 10$ and $\sigma 2 = 2.1$). In all clusters ten patients are included.

11.4.11 Tabulation of individual response data

Not available.

11.4.12 Drug dose, drug concentration, and relationships to response

Not available.

11.4.13 Drug-drug and drug-disease interactions

Not available.

11.4.14 By-patient displays

Not available

11.4.15 Efficacy conclusions

Not available.

12. SAFETY EVALUATION

12.1 Extent of Exposure

Not available

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

No adverse events occurred from observation or due to the sampling of 300 ml of blood.

In heart and lung transplantation patients early after transplantation serious adverse events are expected due to the critical illness. The expected adverse events as described in the study protocol are observed in this observational study, although not due to the bloodsampling. All serious adverse events reported in 16.2.8. are established as not related to tacrolimus side-effects.

Serious adverse events like; death, prolongation of existing inpatients' hospitalization or requiring hospitalization, repeated surgery, significant disability or incapacity, wound complications, serious bleeding (> 1000 ml per day), sepsis, multi organ failure, prolonged mechanical ventilation (>1 day), arrhythmias, pericardial tamponade, severe anemia, disseminated intravascular coagulation, severe electrolyte disturbances, disturbances of proteins, bowel disturbances, weight loss, decubitus, encephalopathy or delirium, pericardial or pleural effusion and pain, are often seen in heart and lung transplantation patients and not due to blood sampling via an arterial catheter. Due to the observational nature of the study, these events are not due to this study and therefore they are not reported separately. They are recorded in the CRF. No adverse events by introducing an arterial catheter, for blood sampling and for continuous blood pressure measurement, are recorded.

Other serious adverse events are reported to the accredited METC. Suspected rejection was observed twice, pancytopenia not due to tacrolimus administration was seen once and in two patients an electrical cardioversion because of arrhythmias was performed. No SUSARs are reported

12.2.2 Display of adverse events

All adverse events displayed were expected in heart and lung transplantation and were not due to the observation or sampling of blood.

Tabel 2. Observed Serious Adverse Events	
Mentioned in list of frequently occurring SAEs	
Death	0
Readmission total	21
Infection	15
Fever	2
Bronchoscopy, bronchial stenosis, laser therapy	5
Gut dysmotility/Distal intestinal obstruction syndrome	3
Implantation of pacemaker	1
Reoccurrence of giant cell myocarditis	1
Venous stent placement	1
Removal of sternum wire	1
Reoperation	7
Serious bleeding >1000 ml	2
Severe anemia	37
Prolonged mechanical ventilation >1 day	23
Severe electrolyte disturbances	34
Severe protein disturbances	26
Wound complications	2
Decubitus grade 3 or more	3
Delirium	3
Arrhythmia for which electrical cardioversion was needed	2
Not mentioned in list of frequently occurring SAEs	
Pancytopenia, medical history of SCID and possibility of thiopurine methyltransferase (TPMT) deficiency	1
Suspected rejection	1

12.2.3 Analysis of adverse events

No adverse events occurred from observation or due to the sampling of 300 ml of blood.

12.2.4 Listing of adverse events by patient

See appendix

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No death occurred. Serious adverse events not mentioned in the study protocol were suspected rejection of patient 3 and 21. Both patients recovered with a combination of methylprednisolone and antibiotics within a week. Rejection is a known side effect of solid organ transplantation. Another serious adverse event is pancytopenia in patient 13. The pancytopenia is related to SCID and/or TPMT combined with critical illness and other drugs than tacrolimus. All SAEs resolved within a few days.

12.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

12.3.1.1 Deaths

No death occurred.

12.3.1.2 Other Serious Adverse Events

None

12.3.1.3 Other Significant Adverse Events

None

12.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

No deaths occurred.

12.3.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

No analyses of death or other serious adverse events is performed.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of individual laboratory measurements by patient (16.2.8) and each abnormal laboratory value (14.3.4)

Not available

12.4.2 Evaluation of each laboratory parameter

Not available

12.4.2.1 Laboratory Values Over Time

Not available.

12.4.2.2 Individual Patient Changes

Not applicable.

12.4.2.2 Individual Clinically Significant Abnormalities

No adverse events occurred from observation or due to the sampling 300 ml of blood.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs of heart and lung transplantation patients early after transplantation are often out of normal ranges, because of the inflammation occurring. Therefore, it is expected that vital signs are beyond the normal range and not due to the administration of tacrolimus or the sampling of 300 ml of blood.

12.6 Safety Conclusions

Critically ill patients, as the heart and lung transplant recipients, are at increased risk for adverse events. In this study no adverse events occurred from observation or due to the sampling 300 ml of blood. None of the patients died during the study.

13. DISCUSSION AND OVERALL CONCLUSIONS

Not available.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Thirty patients are included in the study. Ten patients are heart transplant patients and twenty patients are lung transplant patients. Of the ten heart transplant recipients five are transplanted because of ischemic cardiomyopathy and five because of non-ischemic cardiomyopathy. Non-ischemic cardiomyopathy consists of dilated cardiomyopathy, hereditary dilating cardiomyopathy and giant cell myocarditis. Ten patients underwent lung transplantation because of CF and four because of COPD. The group COPD contains COPD, emphysema, alpha-1 antitrypsin deficiency, hypersensitivity pneumonitis and bronchiectasis. Interstitial lung disease is for six patients the reason for lung transplantation. Interstitial lung disease contains of langerhans cell histiocytosis, sarcoidosis, pulmonary fibrosis, other pulmonary fibrosis, and pulmonary arterial hypertension.

Table3. Demographic data

Table 1. Patients' characteristics			
	N=30 (%)	**Median (IQR)**	**Mean (SD)**
Male	15 (50%)	--	--
Age (yr)	--	43 (34-60)	--
Reason for transplantation			
Heart (**N=10**)			
Ischemic CMP	5 (16.7%)	--	--
Non-ischemic CMP	5 (16.7%)	--	--
Lung (**N=20**)			
Cystic Fibrosis	10 (33.3%)	--	--
COPD	4 (13.3%)	--	--
ILD	6 (20%)	--	--
Double lung transplantation	18/20 (90%)	--	--
SOFA scores per day			
SOFA score		9 (6.8-17)	11.1 (5.9)
Baseline creatinine		66 (53-98)	73.9 (27.7)
ECMO			
Day 1	9 (30%)	--	--
Day 2	8 (26.7%)	--	--
Day 3	5 (19%)		
Day 4	4 (19%)	--	--

Day 5	3 (18%)	--	--
Day 6	3 (18%)	--	--
ECMO duration (days) (**N=8**)		3 (2-6)	3.56 (2.0)

14.2 Efficacy Data

Not applicable

14.2.1 Safety Data

Not applicable

14.2.2 Displays of adverse events

No adverse events due to tacrolimus occurred during the observation period, directly after transplantation.

14.2.3 Listings of deaths, other serious and significant adverse events

No deaths occurred

14.2.4 Narratives of deaths, other serious and certain other significant adverse events

No deaths occurred and no serious adverse effects due to tacrolimus treatment were observed. All serious adverse events resolved.

14.2.5 Abnormal laboratory value listing (each patient)

Not applicable. Individual laboratory measurements by patients are not required by regulator authorities.

15. REFERENCE LIST

Not available.

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

Ammendment: 24/07/2013 The METC of UMC Utrecht approved of the multicentre execution of the study. There was no change in the substantive implementation of the study. Therefore, the last and actual study protocol is attached to this study report.

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

SPARTACUS
(March 2013)

PROTOCOL TITLE

"Pharmacokinetics of tacrolimus in first days after heart and lung transplantation"

Protocol ID	**"SPARTACUS"**
Short title	**Pharmacokinetics of tacrolimus in the first days after heart and lung transplantation**
Version	**007**
Date	**2013/03/06**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee "(ABR = Algemene Beoordeling en Registratie)"
ADQI	Acute Dialysis Quality Initiative workgroup
AE	Adverse Event
AGP	α1-Acid glycoprotein
Alb	Albumin
AR	Adverse Reaction
AUC	Area under the curve
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
Ccr	Creatinine clearance
CF	Cystic Fibrosis
CRF	Case report form
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CL	Apparent clearance of a substance from plasma
CLR	Renal clearance
Cmax	Maximal concentration
CV	Curriculum Vitae
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
EDTA	Ethylenediamine tetra-acetic acid
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
FiO2	Fraction of inspired oxygen in a gas mixture
FKBP	FK506 (=tacrolimus) binding protein
HDL	High density lipoproteins
Hr	Hour
HPLC-MS/MS	High Pressure Liquid Chromatography tandem mass spectrometry
Ht	Hematocrit
IB	Investigator's Brochure
IC	Informed Consent
ICC	Intensive Care Center
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Kg	Kilogram

LUMC	University Medical Center of Leiden
METC	Medical research ethics committee (MREC); in Dutch: "medisch ethische toetsing commissie" (METC)
Ml	Millilitre
NVIC	National Poisons Information Center
NF-AT	Nuclear factor of activated T-cells
PC	Pressure controlled ventilation
Pcr	Plasma creatinine
PEEP	Positive end expiratory pressure
Pg	Page
Pgp	P-glycoprotein
PS	Pressure supported ventilation
(S)AE	(Serious) Adverse Event
SIRS	Systemic inflammatory response syndrome
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
T 1/2	Apparent elimination halve-life
Tmax	Time to reach maximal concentration
Tv	Tidal volume
Ucr	Urine creatinine
UMC	University Medical Center
V	Volume
Vd	Apparent volume of distribution
Wbp	Personal Data Protection Act (in Dutch: "Wet Bescherming Persoonsgevens")
WMO	Medical Research Involving Human Subjects Act (in Dutch: "Wet Medisch-wetenschappelijk Onderzoek met Mensen")

SUMMARY

Introduction and rationale

Tacrolimus is an immunosuppressive agent used as prophylaxis for organ rejection in lung, heart, liver and kidney transplantation. In previous studies, high inter- and intra-individual variability in tacrolimus blood concentration has been observed among transplant recipients. The range and the factors explaining variation in tacrolimus blood concentrations during the first days post-transplantation in heart and lung transplant recipients are largely unknown. More insight on factors causing the inter- and intra-individual variability in tacrolimus concentrations is necessary in order to adapt dose regimen to individuals. Individualization of dosing regimen is needed to prevent organ toxicity, if tacrolimus concentration is too high, and organ rejection, if tacrolimus concentration is too low or in other words, to improve safety of tacrolimus and minimize toxicity directly after heart and lung transplantation.

Objectives

Primary objective:

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

Secondary objectives:

- To show that unbound tacrolimus plasma concentrations can better predict the occurrence of renal dysfunction than whole-blood tacrolimus concentrations.
- Identification of variables influencing the unbound tacrolimus plasma concentrations.
- To evaluate whether variations in tacrolimus concentrations in the first days after lung transplantation in cystic fibrosis patients are higher than without cystic fibrosis.

Long-term objective:

- The data will be used to develop a kinetic model in the future in order to dose tacrolimus more accurately to prevent adverse effects of tacrolimus.

Design

We will perform a multiple doses, open-label, observational, prospective and multi-center study in heart and lung transplant recipients.

Population

Heart and lung transplant recipients admitted to the Intensive Care of a University Medical Center in the first six days post transplantation.

Procedures

Patients will be included at the outpatient's department before the transplantation. Tacrolimus will be administered orally twice a day, according to the usual procedure of the Intensive Care Center. Blood and urine will be collected. Presence or absence of cystic fibrosis will be recorded among lung transplant recipients. Concomitant drugs as a cause of kidney dysfunction will be recorded and plasma concentrations will be measured at steady state. Renal function will also be evaluated in a later phase in de outpatient department after circa 1, 3 and 6 months.

Methods

Blood concentrations of tacrolimus will be measured. Pharmacokinetic analyses will be performed: whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations over time, with determination of maximal concentrations (Cmax) and minimal concentrations (Cmin), time to reach Cmax (Tmax), area under the curve (AUC), apparent elimination half-life (T1/2), apparent clearance of tacrolimus from plasma (CL), and apparent volume of distribution (Vd). The following factors will be studied: plasma proteins (albumin, α1-acid glycoprotein (AGP), and high density lipoprotein (HDL)), erythrocytes concentration in blood (erythrocytes and hematocrit), pH, volume of distribution, genotyping of CYP 3A4/ 3A5 and P-glycoprotein, the existence of digestive tract disorders (ileus or diarrhea), and liver dysfunction or renal dysfunction. Measurement of unbound tacrolimus plasma concentration will be developed at the laboratory of pharmacy of the UMCU. Mixed models will be used to investigate which factors influence whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations. Furthermore, we will study whether there is a relation between whole-blood tacrolimus concentrations and the unbound tacrolimus plasma concentrations versus kidney dysfunction during the first 6 days and at 1, 3 and 6 months post transplantation. Observations will be clustered within patients.

Nature and extent of the burden
Risk: Subjects in this study donate blood in a larger content than in daily practice (circa 50 ml per day with a maximum of 300 ml for 6 days for lung patients as well for heart transplantation patients). At 1, 3 and 6 months an additional 2,5 ml serum per time will be withdrawn. No interventions will be made. No supplementary pain will be caused by extra blood sampling or by urine collection since intensive care patients are already equipped with an arterial line and a urine catheter after lung or heart transplantation and blood sampling in outpatients is standard procedure. Minimal risk is suspected in research subjects.

Benefit: Due to its completeness, this study will be of substantial value for transplantation patients. With the novel knowledge acquired with this study we expect to be able to tailor tacrolimus administration in heart and lung transplantation patients. The result will be less side and toxic effects, and thus an increased patient's safety.

Pharmacokinetics of tacrolimus in first days after heart and lung transplantation

1. INTRODUCTION AND RATIONALE

In The Netherlands, about 70 lung transplantations and 40 heart transplantations are performed every year. Tacrolimus is used as prophylaxis for organ rejection in lung, heart, liver and kidney transplantation. It is usually administered orally, twice a day. High inter- and intra-individual variability in tacrolimus blood concentrations has been observed among transplant recipients. Too low blood concentrations of tacrolimus may result in organ rejection, whereas too high blood concentrations may be toxic and result in organ (renal) dysfunction. Therefore, a correct dosing of tacrolimus is of prognostic importance, especially in critically ill patients.

A specific problem is that pharmacokinetics of drugs in transplanted patients in the days directly after transplantation differ from pharmacokinetics some months or years after transplantation, when the clinical situation of patients is stabilised. For instance, in the first days directly after transplantation, transplanted patients may present a Systemic Inflammatory Response Syndrome (SIRS), especially after a long runtime of extracorporeal circulation. SIRS can cause circulatory instability with multiple organ dysfunction and failure or altered protein metabolism, acid-base imbalance, electrolyte disturbances, activation of coagulation, fluid overload, and diminished haematopoiesis. Most of these alterations can influence pharmacokinetics of tacrolimus separately. In practice, during the days directly after transplantation, tacrolimus dose is adjusted daily, based on whole-blood tacrolimus concentration measured at 6 am. Adjustment of tacrolimus dosing does not take into account the possible pharmacokinetic changes that might have occurred since the measurement of the whole-blood tacrolimus concentration.

Literature reveals that one year after heart and lung transplantation the incidence of renal failure is almost 35%. In our department we observed that kidney dysfunction often starts in the first days after the transplantation and is frequently permanent (unpublished data). Morbidity and mortality after transplantation are for a main part determined by kidney dysfunction. Our hypothesis is that tacrolimus plays a major role in the cause and the course of kidney dysfunction in these patients.

Most research on pharmacokinetics of tacrolimus in transplant recipients has been performed in renal and liver transplant recipients and mostly after a month up to a few years after transplantation (see also appendix 1). However, few studies have focused on heart and lung transplant recipients and, to our knowledge, no studies have been performed so far on pharmacokinetics of tacrolimus in heart or lung recipients directly after transplantation. Unbound tacrolimus plasma concentrations have never been taken into account in these patients. Knowledge about the variables influencing the unbound tacrolimus plasma concentrations in a relevant way may help to identify the patient at risk for inadequate tacrolimus dosing. Inadequate tacrolimus dosing increases the chance for adverse effects.

In this study an extensive number of variables, which may influence the unbound plasma concentrations of tacrolimus, will be determined. By linking changes in these variables to changes in the unbound tacrolimus plasma concentrations it is possible to identify the patient at risk for inadequate tacrolimus dosing. Thus without knowing the unbound tacrolimus plasma concentrations, because it cannot yet be determined in daily practice, it is possible in the future with the knowledge of the results of our study to adjust the

tacrolimus dosing in an indirect way, if the relevant variables are determined influencing the unbound tacrolimus plasma concentrations.

The study will be a one-year long observational study, conducted in heart and lung recipients admitted to the Intensive Care Center of the University Medical Center (UMC) of Utrecht. After inclusion, patients will be followed up to 6 months. Due to its completeness, this study will be of substantial value for transplantation patients. With the novel knowledge developed with this study we expect to be able to tailor tacrolimus administration in heart and lung transplantation patients. The result will be less side and toxic effects, and thus an increase in patient's safety.

2. OBJECTIVES

a. Primary objective:

- To show the greater variability of tacrolimus whole-blood and unbound plasma concentrations during the first 6 days post transplantation compared to the variation of tacrolimus concentrations in stable clinical situation.

b. Secondary objectives:

- To show that unbound tacrolimus plasma concentrations can better predict the occurrence of renal dysfunction than whole-blood tacrolimus concentrations.
- To study which factors influence unbound tacrolimus plasma concentrations in heart and lung transplant recipients (hematocrit, albumin, α1-acid glycoprotein (AGP), and high density lipoprotein (HDL), pH, extensive volume suppletion or CYP3A4/ CYP3A5 and P-glycoprotein (Pgp) polymorphisms, bowel dysfunction or liver dysfunction).
- To evaluate whether variations in tacrolimus concentrations in the first days after lung transplantation in cystic fibrosis patients are higher than without cystic fibrosis.
- The data will be used to develop a kinetic model in the future in order to be able to adjust the tacrolimus dose to the individual patient to prevent or reduce adverse effects of tacrolimus.

3. STUDY DESIGN

We will perform a prospective, multi center, observational, open label study in heart and lung transplant recipients admitted to the Intensive Care Center of the University Medical Center of Utrecht. Pharmacokinetic parameters will be observed in 30 heart and lung transplant recipients up to the first 6 days after transplantation or shorter if patients are discharged from the intensive care earlier. Renal function will be evaluated in the first days and circa 1, 3 and 6 months after transplantation in the out-patient department.

4. STUDY POPULATION

a. Population

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

Lung transplantation patients will be patients with and without cystic fibrosis. These transplantations are performed with or without extracorporeal circulation. Heart transplantation will always be performed with extracorporeal circulation.

b. Inclusion criteria

- Patients ≥ 18 years
- Patients admitted to the ICC of UMCU after heart or lung transplantation
- Treated with tacrolimus (Prograft®; Astellas Pharma Europe)
- Informed consent obtained

c. Exclusion criteria

- Patients < 18 years
- Patients who die within one day after admission to the ICC of UMCU
- Withdrawal of informed consent
- Allergy towards tacrolimus or macrolides
- Patients on total parenteral nutrition

d. Sample size calculation

Practically, in such pharmacokinetic studies, a relatively small group of subjects (e.g, 6-12) is often included. A sample size calculation has been performed showing that the minimum sample size is 5 patients per sample (with a 90% confidence and a 95% power). In our center, about 20 lung transplantations and 10 heart transplantations are performed per year. A one-year study would therefore be long enough to include 10 patients per subgroup (10 patients with heart transplantation, 10 patients with lung transplantation and cystic fibrosis, 10 patients with lung transplantation and no cystic fibrosis). For the pharmacokinetic modelling part of the study, we expect to have between 300-600 whole-blood tacrolimus concentrations available per group (between 3 and 6 days of stay at the Intensive Care Unit, 10 blood samplings per day, 10 patients), and between 90-180 unbound tacrolimus plasma concentrations available per group (between 3 and 6 days of stay at the Intensive Care Unit, 3 blood samplings per day, 10 patients).

5. INVESTIGATIONAL MEDICINAL PRODUCT

a. Name and description of investigational medicinal product

Tacrolimus (FK506, Prograft®, Advagraf®) is a 23-membered ring, 822 Dalton macrolide, which is isolated from the fermentation broth of Streptomyces Tsukubaensis and was discovered in 1984 in Tsukuba, Japan *1*. It is a calcineurin inhibitor and is used as prophylaxis for organ rejection in lung, heart, liver and kidney transplantation. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus

binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression) *2*.

b. Summary of findings from clinical studies

b.a. Pharmacokinetics of tacrolimus in general

Pharmacokinetics in transplantation patients in the first days after surgery differ from pharmacokinetics in healthy persons or transplantation patients in a later and clinically stable phase. Correct dosing is therefore often difficult to perform. Directly after transplantation, transplanted patients are often characterized by inflammation which can cause organ failure, fluid overload, altered protein metabolism, acid-base imbalance, electrolyte disturbances, activation of coagulation, diminished haematopoiesis, etc. Causes are long surgery period with extracorporeal circulation, ischemia or acute rejection of transplanted organ(s), massive blood transfusions or infection. The inflammatory response is manifesting as SIRS. SIRS can lead to circulatory instability with respiratory distress depending on the intensity of the host response, developing to multiple organ dysfunction and/or failure. In almost all patients SIRS criteria are met directly after transplantation and decrease mostly in a few days spontaneously. Due to the above mentioned changes, there can be altered drug bioavailability, distribution, metabolism and reduced hepatic or renal clearance.

Absorption: Tacrolimus is administered orally and its absorption is hardly predictable due to various factors like fasting, diarrhea or ileus or altered P-glycoprotein (PgP) and CYP3A activity in the gut *3-7*. Oral bioavailability of tacrolimus varies from 5 to 32% *8-15*. (see also pg 12,13, 18 appendix 1)
Distribution: In blood, tacrolimus is mainly accumulated within erythrocytes (85%) followed by binding to plasma proteins like albumin, AGP and high-density lipoprotein (HDL) (14%). The percentage of tacrolimus accumulated within the erythrocytes and bound to proteins is dependent on their blood concentrations which often change after transplantation *8-13*. Binding to plasma proteins can change in case of hypoalbuminmia due to capillary leakage or diminished production or in case of renal dysfunction due to decreased plasma protein concentrations, conformational changes in albumin molecule and competitive binding of toxins and acids to albumin *13*. Pharmacokinetics of tacrolimus is further influenced by fluid administration, probably resulting in a wide range in blood concentrations due to dilution of the drug and acidity of whole-blood. (see also pg 7 up to and including 11 and 18 and 19 appendix 1)
Metabolism: Tacrolimus is extensively metabolized in the liver and gut by CYP3A4 and CYP3A5, which can be influenced by gene expression and interactions with other drugs (see pg 12-13 and 19-20 appendix 1 and appendix 2). There are many known interactions of different kinds of drugs with tacrolimus, which can alter tacrolimus blood concentrations significantly (see appendix 2).
Excretion: Biliary excretion is thought to be the major route of the elimination of tacrolimus metabolites *16*.

Cystic fibrosis (CF): Pharmacokinetics in CF patients is different from non-CF patients. In this patient group, the extent of drug absorption varies widely and the rate of absorption is slower. Absorption of tacrolimus through the gastrointestinal tract may be impaired due to fat malabsorption because of pancreatic insufficiency. In a study it has been seen that CF patients require higher doses of tacrolimus than those without CF to achieve similar drug concentrations. A longer time to peak concentration (Tmax) and a prolonged half life time (T1/2) are seen in CF patients *14*. Due to hepatic dysfunction, patients with CF have enhanced clearance of many, but not all, drugs *15*. This may be the consequence of disease-specific changes in both enzyme activity and/or drug transport within the liver *15*. There are no studies that describe hepatic clearance of tacrolimus in CF patients. Also, the renal clearance (CLR) of many drugs in patients with CF is enhanced although no pathological abnormality is identified which could explain this finding: glomerular filtration rate and tubular secretion appear normal in patients with CF. It is unknown whether tacrolimus pharmacokinetics is influenced by changes in renal clearance. It is advised for population modelling to compute renal clearance and hepatic clearance in CF and non-CF patients separately *17, 18*. (see pg 13 and 14 appendix 1)

Changes in absorption, distribution, metabolism and clearance can influence the inter- and intra-individual variability in tacrolimus concentrations. We will carry out a study of the pharmacokinetics of whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations in heart and lung (CF and non-CF) transplant recipients in the first days after transplantation with a follow up period of approximately 6 months. With the results of this study, insight in pharmacokinetics of tacrolimus in transplantation patients directly after transplantation will be improved. This knowledge will be advantageous for the correct dosing of tacrolimus, which optimizes patient's safety.

b.b. Pharmacokinetics in transplant recipients immediately or several days after transplantation

Few studies have been conducted to investigate the pharmacokinetics of tacrolimus in transplant recipients immediately or several days after transplantation *16, 19, 20*.

In the first study whole-blood and urine concentrations of tacrolimus and its metabolites were measured in seven liver transplant patients after a first oral dose equal to 0.04 mg/kg *19*. The first dose was given at 6 hours after revascularisation of the liver graft. Blood drug concentrations were described by an open two compartment model with first-order absorption. Kinetic parameters were as follow (means): Tmax = 1.9 hr, Cmax = 17.4 µg/L, AUC0-12hr = 328.1 µg.hr/L, T1/2initial = 0.74 hr, T1/2terminal = 26 hr.

The second study aimed to investigate the relationship between therapeutic whole-blood tacrolimus concentrations and the inhibition of calcineurin *20*. In this study, whole-blood tacrolimus concentrations were measured in twenty-one renal transplant patients at day 3 and day 14 post-transplantation. All patients had blood sampled prior to the ingestion of tacrolimus to measure the trough level i.e. 12 hr after the previous dose of tacrolimus. Blood sampling took also place at 1, 2, 3, 4 and 6 hours following the ingestion of 0.1 mg/kg of tacrolimus. The dose of tacrolimus received by each patient was adjusted according to the standard target drug levels for tacrolimus in this hospital, i.e.10-20 µg/L. At day 3, mean whole-blood tacrolimus trough concentration was 13 µg/L, (SE = 1.15), and mean whole-blood tacrolimus peak concentration was 30 µg/L, (SE = 3.51) and 16.9 µg/L, (SE = 1.84) at respectively 1 hour and 6 hours after ingestion of tacrolimus.

A third study investigated the blood distribution and protein binding of tacrolimus in liver transplant recipients over the first 60 days after transplantation *21*. Blood samples were collected from 10 liver transplant recipients on days 1, 7, and 60 after the initiation of tacrolimus therapy, and the distribution of tacrolimus in blood and the plasma protein binding were investigated. The tacrolimus amount in the erythrocytes varied significantly (74 vs 80 % of total whole-blood concentration) from day 1 to day 60. The percentage of tacrolimus within leukocytes (1.10 % vs 0.40% of total whole-blood concentration) and the unbound concentration of tacrolimus (0.70 vs 0.28 ng/L) were significantly lower during episodes of rejection. In patients experiencing tacrolimus-related side effects, only the unbound tacrolimus concentration was found to be significantly higher (0.84 vs 0.53 ng/L) and whole-blood tacrolimus concentrations were within the therapeutic range (9.2 vs 8.1 µg/L). Blood distribution and protein binding of tacrolimus vary significantly over the post transplantation period.

According to the www.clinicaltrials.gov website of the U.S. National Institute of Health (search terms: 'tacrolimus' and 'pharmacokinetics' and 'transplantation'), there is a study running to compare the pharmacokinetics of tacrolimus in adult heart transplant recipients treated with Advagraf® or Prograf® (NCT01332201). It is a phase II, open label, parallel group, multi center study to compare pharmacokinetics of tacrolimus in adult subjects undergoing primary allograft transplantation receiving a once daily or twice daily based immunosuppressive regimen, including a long term follow-up. Blood is sampled at days 1, 3, 7 and 42. The primary outcome is AUC24 to determine steady state concentrations. Secondary outcomes are Cmax, Tmax, C24, rejection episodes, subject survival and graft survival. To the best of our knowledge, there are no studies underway that are similar to the proposed study.

c. Summary of known and potential risks and benefits

Potential risks in this study are the same of those that can be expected with the normal use of tacrolimus: Principle adverse effects associated with tacrolimus include nephrotoxicity, neurotoxicity (headache, mild tremors, photophobia, and dizziness), diabetogenesis (hyperglycaemia, post-transplant diabetes), gastrointestinal disturbances (nausea, vomiting, diarrhea or ileus), hypertension, mild hyperkalaemia, and infections *22*. Rare adverse effects associated with tacrolimus include allergic reaction (pruritus, alopecia), haematological effects (anaemia), optic neuropathy, psychiatric effects (feeling jittery, nightmares, and insomnia), cardiovascular disorders (arrhythmia, chest pain), and hyperlipidemia. Very rare adverse effects associated with tacrolimus include an increased risk of malignancy, especially lymphoma. Early after transplantation the most seen toxicity is nephrotoxicity. (see also pg 24 up to 27 appendix 1)

Potential benefit: Due to its completeness, this study will be of substantial value for transplantation patients. With the novel knowledge developed with this study we expect to be able to tailor tacrolimus administration in heart and lung transplantation patients. The result will be an increasing efficacy and less side and toxic effects, and thus an increase in patient's safety.

d. Description and justification of route of administration and dosage

Tacrolimus (Prograft®) will be given orally. The starting dose will be a total of 0.1 mg/kg bid. These are the current route and dose of tacrolimus administration at the Intensive Care Department.

e. Dosages, dosage modifications and method of administration

Adjustment can be necessary to achieve a whole-blood tacrolimus concentration of 9 - 16 µg/L. The tacrolimus dose will be adjusted by the attending physicians according to the trough tacrolimus blood concentration measured the previous day at 6 am. The result of the extra tacrolimus analyses will not be communicated to the physicians in order not to interfere with normal daily practice. This study is an observational study and not an intervention study.

6. METHODS

a. Main study parameters

- The main study parameters are whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations together with the pharmacokinetic parameters: AUC, Cmin, Cmax, Tmax, T1/2, Vd, CL, CL/F (=oral clearance).

b. Secondary study parameters

- Renal dysfunction: The AKIN classification will be used to quantify renal function in intensive care: stage 1, 2 or 3 (see Table 1). Renal failure will be assessed also by 24 hours creatinine clearance. If renal replacement therapy was initiated this will be recorded in CRF (See also appendix 1 pg 5 and 6)
- Erythrocytes (see also appendix 1 pg 7 and 18 and 19)
- Hematocrit: defined as the percentage of red blood cells in whole-blood, normally about 35-40%. (see also appendix 1 pg 18 - 19)
- Albumin (see also appendix 1 pg 7 - 9, 18 and 19)
- α1-Acid glycoprotein: AGP is an acute phase protein. The serum concentration of AGP raises several folds during an acute phase response, the systemic answer to a local inflammatory stimulus. Also, its glycosylation pattern can change depending on the type of inflammation. The biological function of this protein is not clear. A number of activities on different types of blood cells have been described. In vivo, AGP clearly has protective effects in several models of inflammation. (see also appendix 1 pg 9 and 10, 18 and 19)
- High density lipoprotein (see also appendix 1 pg 10 and 11, 18 and 19)
- pH (see also appendix 1 pg 19)
- Daily fluid balance and body weight (see also appendix 1 pg 11)
- CYP3A4/CYP3A5 polymorphisms, and P-glycoprotein polymorphisms (see also appendix 1 pg 12 and 13, 19)
- Hepatic dysfunction: bilirubin and ALAT will be used to quantify hepatic dysfunction (See also appendix 1 pg 6 and 7)
- Diarrhea or ileus (see also appendix 1 pg 18)
- Cystic fibrosis (See appendix 1 pg 13 and 14)
- Plasma concentrations of (val)acyclovir, (val)ganciclovir, tobramycin and trimethoprim/sulfamethoxazole, if administered, will be measured at steady state as possible additional factor causing kidney dysfunction

c. Other study parameters

Other study parameters (which may influence the pharmacokinetics of the whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentration) are:

- Systemic Inflammatory Response Syndrome

- APACHE-IV and SOFA for determination of severity of illness
- Continuous Renal Replacement Therapy (CRRT)
- Concomitant medication, including contrast media, will be registered and evaluated

c.a. Explanation of definitions

Renal dysfunction:

Renal dysfunction is classified by the modified RIFLE criteria the so called AKIN criteria formulated by the Acute Kidney Injury Network. Classification consists of stage 1, 2 and 3 (see table 1). (See also pg 5 and 6 of appendix 1)

Tabel 1. AKIN criteria

phase	Serum creatinine criteria	Criteria on basis of diuresis
1	Increase in serum creatinine ≥26 µmol/L or 150-200% from baseline	Urine <0,5 ml/kg/hr for >6 hours
2	Increase in serum creatinine >200-300% from baseline	Urine <0,5 ml/kg/hr for >12 hours
3	Increase in serum creatinine >300% or ≥354 µmol/L with an acute increase of at least >44 µmol/L	Urine <0,3 ml/kg/hr for >24 hours or anuria >12 hours

Renal clearance will be calculated as 24 hours creatinine clearance:

$$Ccr\ (ml/min) = \frac{Ucr\ (\mu mol/L) \times V\ (L/24\ h)}{Pcr\ (\mu mol/L)}$$

Hepatic dysfunction:

Liver tests consist of assessment of alanine aminotransferase (ALAT) and bilirubin. If one of these two tests is increased two times above the upper limit, it is defined as liver damage. Serum ALAT of more than twice the upper limit (for men 90 U/L and for women 70 U/L) and bilirubin of >34 µmol/L will be used as biomarkers for hepatic damage in this study (see also pg 6 and 7 of appendix 1).

SIRS criteria:

SIRS is defined as 2 or more of the following criteria are present: a body temperature lower than 36°C or higher than 38°C, heart rate above 90 beats/min, respiratory rate above 20/min or PaCO2 of less than 32 mmHg and white blood cell count lower than 4 X 10 9/L or higher than 12 X10 9 /L or >10% bands. Temperature will be measured centrally (rectal, nasal or at the tip of a pulmonary artery catheter).

APACHE IV-score:

The Acute Physiology and Chronic Health Evaluation IV score (APACHE-IV) uses information on physiological variables next to age, surgical status and previous health status. It uses the worst values during the first 24 hours in the ICU for 12 physiological variables weighted from 0 to 4 points according to degree of change from normal values. Although the APACHE IV model uses the same physiological variables and weights as APACHE III and II, it is more complex (142 variables), mainly due to expansion in the number of disease groups (from 94 to 116) and new predictor variables. The score allows estimating the probability of hospital mortality. The APACHE IV model has a good performance in the Dutch ICU population *23*. (see also pg 4 of appendix 1)

SOFA-score:
The Sequential Organ Failure Assessment (SOFA) score can help assess organ dysfunction or failure over time and is useful in evaluating morbidity. The score is designed to be applied daily throughout the ICU stay. 6 Physiological variables (respiratory, cardiovascular, renal, liver, central nervous system and coagulation) are measured. Scores are from 0 to 24. (see also pg 4 of appendix 1)

d. Study procedures
Patients fulfilling the inclusion and not the exclusion criteria will be included after the nature and purpose of the investigation will have been explained to them, and after they have signed a study specific informed consent form.

Pre-study:
Measurement of unbound concentrations of tacrolimus:
Before starting the study, the method of measurement of unbound concentration of tacrolimus, will be tested *10, 24*. (appendix 1 pg 17)

Main study:
Before transplantation:
After signing the informed consent form, and before the transplantation, the following procedures will be applied:

- Collection of demographic data (age, gender, weight, length, and attribution of a Unique Trial Number).
- Recording of medical history, indication of transplantation (heart or lung failure, Cystic Fibrosis or not), and pre-existent renal dysfunction or not.

After transplantation:
Directly after transplantation and after arrival at the Intensive Care Center the following procedures will be applied:

- Day 1 is defined as the day of admission to the intensive care, day 2 to day 6 are defined as the days following the admission to the intensive care. Discharge can take place either on day 2, 3, 4, 5 or 6. In case of discharge before day 6 the observation will stop.
- Clock time at which first tacrolimus administration at the intensive care starts will be recorded in the CRF. Every day at 6 am and 6 pm tacrolimus will be administered. Dosing will be done by the attending physicians according to daily practice; starting with 0.1 mg/kg/day divided in 2 doses, thereafter based on whole-blood total tacrolimus concentrations of 6 am. Whole-blood tacrolimus concentrations of 6 am will be shown to the attending physician. All other measurements of tacrolimus will not be revealed to the caretakers.

- Whole-blood tacrolimus concentrations will be measured prior to dosage (t=0 hours; baseline) and at t = 1, 1 ½, 2, 2 ½, 3, 4, 6, 8, and 12 hours after each tacrolimus administration at 6 pm for a maximum of 6 days until discharge of the Intensive Care Unit. The unbound tacrolimus plasma concentrations will be measured at 0, 2 and 6 hours after each tacrolimus dose at 6 pm for non-CF patients and at 0, 3 and 6 hours after each tacrolimus dose at 6 pm for CF patients. Every day at 6 pm the following blood samples will be drawn for measurements of biochemical, haematological and other parameters: (tables 2 and 3), Kidney function (urea, creatinine) and liver function (bilirubin, ALAT) will be measured at 6 am as daily routine for 6 days. When patients are discharged to the ward before day 6 routinely measured urea and creatinine will be recorded in the CRF. Whole-blood tacrolimus concentrations at 6 am (the so-called 'trough' whole-blood tacrolimus concentration) will be analysed every day and the treating physician will be informed about the results. The remaining whole-blood tacrolimus concentrations and unbound tacrolimus plasma concentrations will be analysed afterwards in a batch per 6 months and will not be available to the treating physician.
- Blood will be drawn from an arterial line catheter which is already inserted in every patient in current daily practice. The study parameters mentioned in paragraphs 6a, 6b and 6c will be recorded in the CRF.
  The following parameters will also be recorded in the CRF: 24 h creatinine clearance, urine output, temperature, heart frequency, respiratory rate, setting parameters of mechanical ventilation (Pressure control/Pressure support, inspiratory plateau pressure/PEEP, FiO2, tidal volume). The parameters for blood analyses are shown in Table 3. The routine parameters will be performed according to standard analyses.

  The following blood collecting tubes will be used: Li-heparin gel (light green) 3 mL, EDTA (pink) 1 mL, EDTA (pink) 2 mL, EDTA (purple) 3 mL, EDTA (purple) 5 mL, 0.5 ml Sarstedt cryovials (for α-1-acid glycoprotein 1 mL). Each blood sample will be given a barcode with the Unique Trial Number. All samples 0 – 64 and month 1,3 and 6 per unique trial number will be collected and send to the laboratory as soon as possible (otherwise stored at -80 °C until transport). Samples for measurement of α-1-acid glycoprotein per unique trial number will be centrifuged immediately (1500 g) and plasma prepared from these samples will be stored in 0.5 mL vials (Eppendorf vials) at -80 °C until assay measurement.
- To measure 24 h creatinine excretion in every patient, urine will be collected 24 hours a day for a maximum of 6 days until discharge from the intensive care unit. A urine catheter is already introduced in every patient for routine care. Urine collectors will be stored and analyzed by the clinical chemical laboratory of UMCU.
- Plasma concentrations of (val)acyclovir, (val)ganciclovir, tobramycin, if administered, will be measured at steady state on day 3 and 6 before and 3 hours after administration and plasma concentrations of sulfamethoxazole will be measured on day 3 at steady state before administration.
- APACHE (acute physiology and chronic health evaluation score) and SOFA score (sequential organ failure assessment score), both severity of disease classification systems, will be recorded on the intensive care, for APACHE 24 hours after admission and for SOFA score once a day.

- After circa 1, 3 and 6 month at the out-patient department :

Plasma urea and plasma creatinine will be measured and recorded in the CRF for each patient after circa 1, 3 and 6 months. Urine will be collected for 24 hours to calculate creatinine clearance.
In case of kidney dysfunction, plasma concentrations of concomitant drugs (e.g. sulfamethoxazole, valganciclovir, intravenous colistine, azitromycin, amfoB) will also be analysed.

Table 2. Blood analyses and estimated blood sampling amount during the study

A. Li-heparin gel (light green), 3 mL	**Biochemical parameters**	
	# Bilirubin	
	# Urea	mg/L
	# Creatinine	
	# C-reactive protein (CRP)	
	# Albumin	g/L
	# HDL	mmol/L
B. EDTA (pink), 2 mL	**Haematological parameters**	
	# Erythrocytes	10^{12}/L
	# Hemoglobin	mmol/L
	# Hematocrit	fraction
	# Tot. leukocyte count	10^{9}/L
	# Dif. leukocyte count	%
	Other parameters	
C. Blood gas syringe 3ml; 1,5 ml	# pH	
D. EDTA (pink), 1ml	# Tacrolimus whole-blood	µg/l
E. EDTA (purple), 10 ml	# Tacrolimus unbound concentration	µg/l
F. EDTA (pink), 1 ml	# Serum	
G. Heparin (microvial), 1ml	# AGP	g/l
H. EDTA (purple), 3ml	# Cyp 3A4/CYP3A5/PgP	g/l
I. EDTA (pink), 1ml	# Ganciclovir/Acyclovir/Sulfamethoxazol	mg/l
J. Serum (yellow), 0,5 ml	# Tobramycin	mg/l

Blood samples volume regular measurements UMC Total amount blood volume tacrolimus study			
	sampling tubes	**total volume in ml for study**	**total volume in ml for regular measurement**
tacrolimus whole-blood	60 D	54	6
tacrolimus unboud fraction	18 E	180	
Biochemical/Haematological	7 A/B	35	
pH	6 C	9	
AGP	6 G	6	
serum	7 F	7	

Cyp3A4/cyp3A5/Pgp	1 H	3	
Ganciclovir/Acyclovir/Tobramycin	2 I	4	
Sulfamethoxazole	1 J	2	
		300 ml	**6 ml**

Table 3. Schedule of blood sampling and tacrolimus administration

actual time	Day 1 6:00 AM	Day 1 6:00PM	6:05 PM							Day 2 12:00 AM		6:00 AM	6:05 AM
scheme time	-12	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	0	1		2	3	4	5	6	7	8	9	10	
administration of tacrolimus	x		x										x
tacrolimus whole blood	o	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction		x/ x CF				x		x CF		x/ x CF			
biochemical/haematological		x											
pH		x											
AGP		x											
serum		x											
Cyp3A4/cyp3A5/Pgp		x											
Ganciclovir/Acyclovir/Tobramycin													
Sulfamethoxazole													

o: 1ml of blood will be withdrawn for baseline measurement if the patient starts with tacrolimus at 6 AM

actual time	Day 2 6:00 PM	6:05 PM							Day 3 12:00 AM		6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	11		12	13	14	15	16	17	18	19	20	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 3 8:00 AM		11:00 AM
scheme time	14		17
vial number	21		22
administration of tacrolimus			
tacrolimus whole blood			
tacrolimus unbound fraction			
biochemical/haematological			
pH			
AGP			
serum			
Cyp3A4/cyp3A5/Pgp			
Ganciclovir/Acyclovir/Tobramycin	x		x
Sulfamethoxazole	x		

actual time	Day 3 6:00 PM	6:05 PM							Day 4 12:00 AM		6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	23		24	25	26	27	28	29	30	31	32	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 4 6:00 PM	6:05 PM							Day 5 12:00 AM		6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	33		34	35	36	37	38	39	40	41	42	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 5 5:55 PM	6:00 PM							Day 6 12:00 AM		6:00 AM	6:05 AM
scheme time		0	1	1,5	2	2,5	3	4	6	8	12	
vial number		43	44	45	46	47	48	49	50	51	52	
administration of tacrolimus	x											x
tacrolimus whole blood		x	x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction		x/ x CF			x		x CF		x/ x CF			
biochemical/haematological		x										
pH		x										
AGP		x										
serum		x										
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

actual time	Day 6 8:00 AM		11:00 AM
scheme time	14		17
vial number	53		54
administration of tacrolimus			
tacrolimus whole blood			
tacrolimus unbound fraction			
biochemical/haematological			
pH			
AGP			
serum			
Cyp3A4/cyp3A5/Pgp			
Ganciclovir/Acyclovir/Tobramycin	x		x
Sulfamethoxazole	x		

	Day 6								Day 7			Day 7
actual time	6:00 PM	6:05 PM							12:00 AM		6:00 AM	6:05 AM
scheme time	0		1	1,5	2	2,5	3	4	6	8	12	
vial number	55		56	57	58	59	60	61	62	63	64	
administration of tacrolimus		x										x
tacrolimus whole blood	x		x	x	x	x	x	x	x	x	x	
tacrolimus unbound fraction	x/ x CF				x		x CF		x/ x CF			
biochemical/haematological	x											
pH	x											
AGP	x											
serum	x											
Cyp3A4/cyp3A5/Pgp												
Ganciclovir/Acyclovir/Tobramycin												
Sulfamethoxazole												

xCF in cystic fibrosis patient samples wil be withdrawn one hour after patients without Cystic fibrosis

	month 1
administration of tacrolimus	x
tacrolimus whole-blood	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

	month 3
administration of tacrolimus	x
tacrolimus whole-blood	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

	month 6
administration of tacrolimus	x
tacrolimus whole-blood	x
creatinine clearance	x
Ganciclovir/Acyclovir/Tobramycin	v
Sulfamethoxazole	v

V: in case of kidney dysfunction

The estimated maximum amount of blood required during the first days of the study is 300 mL (ca 50 ml per day) (Table 2). In case of renal dysfunction, at circa 1, 3, and 6 months an additional 2,5 ml of blood might be required. Clinical laboratory and tacrolimus samples collected during this study will be analysed by the pharmaceutical laboratory UMCU (Utrecht, The Netherlands). Samples for measurement of unbound tacrolimus plasma concentration will be stored at -80°C and will be analysed afterwards at the laboratory of UMCU in batches per approximately 6 months. Serum samples for AGP measurement will be stored at -20°C and analysed by the laboratory of University Medical Center of Leiden (LUMC). Samples Cyp3A4/Cyp3A5/Pgp will be analysed by the laboratory of the Department Clinical Chemistry (AKC) of Erasmus Medical Center. The Investigator will maintain on file, written evidence that these facilities are certified/accredited under applicable regulations. Residual plasma samples will be stored at -80 °C and will possibly be used at later time points (within 5 years).

Liquid Chromatography–Tandem Mass Spectrometry Instrumentation (LC MS/MS) a liquid chromatography system comprising of auto sampler and micro pumps (Thermo Fisher Scientific) will be used for tacrolimus quantification. The lower limit of quantification (LOQ) for tacrolimus is 0.5 µg/L. The interday variability of the tacrolimus measurements is <5%, secured by the pharmaceutical laboratory UMCU. Clinical laboratory assays will be performed according to standardised procedures. All assays are validated according to the guidelines set by CCKL.

e. Procedures throughout the study period
Adverse events (AEs) will be registered in the CRF throughout the study period. To facilitate summarizing of AEs, reported AE terms will be coded to a standard set of 'preferred terms' as defined in the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence and the incidence of possible or probable tacrolimus-related events will be summarized (including statements on the severity of events). An adverse event that occurred during the observation period (6 days after transplantation) or at follow-up (up to 6 month after transplantation) will only be counted as an adverse event if it was either not present at baseline or it was present at baseline but increased in severity during the treatment period.

f. Withdrawal of individual subjects
In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason if they wish to do so without any consequences. The Investigator also has the right to withdraw participants from the study. Subjects may be withdrawn from the study for the following reasons:
1. Adverse Events;
2. Inter-current illness that, in the judgment of the Investigator, might invalidate the study or place the participant at risk;
3. At the request of the volunteer or principal Investigator
4. Due to protocol violations or unreliable behaviour.

If the reason for withdrawal of a subject from the study is an adverse event, the principal specific event and any related test results will be recorded in the CRF. When a subject is withdrawn from the study, all observations collected up to the time of termination will be recorded in the CRF along with the reason for termination.

7. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

a. Adverse and serious adverse events
Adverse events by introducing an arterial catheter, for blood sampling and for continuous blood pressure measurement, will be recorded, which are for instance infections or haemorrhage from the arterial catheter (> 200 ml per day). Because an arterial line is already inserted and low risk is expected in this observational study, they will be reported once per 6 months. All SUSARs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol.

Serious adverse events like; death, prolongation of existing inpatients' hospitalisation or requiring hospitalisation, repeated surgery, significant disability or incapacity, wound complications, serious bleeding (> 1000 ml per day), sepsis, multi organ failure, prolonged mechanical ventilation (>1 day), arrhythmias, pericardial tamponade, severe anaemia, disseminated intravascular coagulation, severe electrolyte disturbances, disturbances of

proteins, bowel disturbances, weight loss, decubitus, encephalopathy or delirium, pericardial or pleural effusion and pain, are often seen in heart and lung transplantation patients and not due to blood sampling via an arterial catheter. Due to the observational nature of the study, these events will not be due to this study and therefore they will not be reported separately. They will be recorded in the CRF.
Other serious adverse events if not mentioned before will be reported to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse event. All SUSARs will be reported through the web portal *ToetsingOnline* to the accredited METC.

b. Follow-up of adverse events
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8. PHARMACOKINETIC AND STATISTICAL ANALYSES

a. Concentration over time curves
The following concentration-time curves will be derived for each patient for the 6 days (or less if the patient is discharged earlier from the intensive care unit):

- 12-Hour whole-blood tacrolimus concentrations.
- 12-Hour unbound tacrolimus plasma concentrations.

Using these curves, the distribution for tacrolimus concentrations will be evaluated. Standard deviations will be used to quantify the variability in tacrolimus concentrations. If the distributions of the tacrolimus concentrations are asymmetric, data will be transformed, for instance by taking the logarithms of the data.

The variance in tacrolimus trough concentrations in whole-blood of stable patients is known from the literature (8.4 µg/L with a standard deviation (SD) of 2.1 at 6 months post-transplantation *25*. An F test will be used to compare the variance in our study (sigma 1 squared) with the variance found in the literature for stable patients (sigma 2 squared). We expect the SD of tacrolimus trough concentration in whole-blood at day 4 to be minimum 5 times larger than at 6 month post-transplantation (so at least a SD>10, estimation based on own unpublished data, at day 4: mean tacrolimus concentration of 18.3 µg/L with a SD of 12.3 µg/L). The F test will be used to compare the two variances: the variance in the present study ($\sigma 1$) squared with the variance found in the literature ($\sigma 2$) squared. The null hypothesis is that both variances are equal. The alternative hypothesis is that $\sigma 1$ is larger than $\sigma 2$ (upper one-tailed test).

A sample size calculation has been performed showing that the minimum sample size is 5 patients per sample (with a 90% confidence and a 95% power for an estimated $\sigma 1 = 10$ and $\sigma 2 = 2.1$).

b. Pharmacokinetic modelling
Kinetic parameters for whole-blood tacrolimus concentrations will be calculated: AUC, Cmax, Cmin, Tmax, T1/2. Pharmacokinetics of tacrolimus will be analyzed by nonlinear mixed-effects modelling (in NONMEM or R). A nonlinear mixed-effects model consists of two sub-models: a structural model (fixed effects) and a stochastic model (random effects). Both the structural and stochastic parameters are simultaneously estimated by fitting the model to the data.

The structural model will describe the relationship between dose and concentration in terms of structural pharmacokinetic parameters (i.e. volume of distribution (Vd), clearance (CL)).
The stochastic model will describe the random variability in the structural model parameters. One kind of random effects is the interindividual variability (unexplained differences between individuals due to biology, for instance). Interindividual variability describes the random variability of structural parameters within the population.
Another kind of random effects is the inter-occasion variability in case of repeated measurements. Inter-occasion variability describes the variability of an individual parameter value from one occasion to another.
A second level of stochastic effects describes the variability of the difference between observed and predicted response ($\sigma 2$, variance of the residual error). $\sigma 2$ includes among other factors, model misspecification, intra-individual variability, and measurement error.

c. Covariate analyses
One of the important aims in population pharmacokinetic modelling is the establishment of relationships between parameters and covariates (i.e. patient specific variables) to explain parameter variability and facilitate dose adjustment decisions.
Descriptive statistics of the following covariates, selected on the basis of their known or theoretical relationships with pharmacokinetics of tacrolimus, will be performed: hematocrit, SIRS, APACHE-score, SOFA-score, pH, albumin, α1-acid glycoprotein, high density lipoprotein, diarrhea or ileus, liver and renal functions, continuous renal replacement therapy, fluid balance or body weight, possible drug-drug interaction with concomitant medication, cystic fibrosis, polymorphisms in CYP3A4, CYP3A5 and P-glycoprotein.
The search for important covariates is not straightforward, especially if there are large numbers of covariate-parameter relations to consider. Covariate models will be built for identifying candidate covariate effects and to test the importance of found covariate terms, according to the so-called "stepwise covariate model building strategy" *26*. The obtained minimum value of the objective function (MVOF) defined as minus twice the log likelihood will be used for model comparisons.

d. Other statistical analyses
Mixed models will also be used to study the relationship between renal dysfunction and the trough whole-blood tacrolimus concentration, and between renal dysfunction and the trough unbound tacrolimus plasma concentration. Observations will be clustered within individuals. Possible confounders like the use of extracorporeal circulation or the kind of transplantation will be included in the analyses.

9. ETHICAL CONSIDERATIONS

a. Regulation statement
The study will be conducted according to the principles of the Declaration of Helsinki (version 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). By signing this protocol the investigators commit themselves to conduct this study in according to Good Clinical Practice.

b. Recruitment and consent
All heart or lung transplantation patients will be asked prior to surgery, if they are willing to participate in the study by the study nurse or one of the investigators. If they are interested in study participation, they will receive written information on the study.

The patient will then be given adequate time, at least 24 hours, to read the information and sufficient opportunity to ask the study nurse or one of the investigators any questions. Thereafter, the patient will be informed orally about the study proposal, schedule and (dis-)advantages. The patient should not enter the study if he/she has not understood the written and verbal information provided and/or if there is no signed and dated consent form. A copy of the written information and the signed informed consent will be provided to the participant, whereas the original version will be retained by the investigator. When the patient is capable of understanding the informed consent, he or she will be asked to give personal informed consent. The patient can object and this patient will be withdrawn from the study.

The inclusion and exclusion criteria for enrolment in the study are detailed in paragraphs 4b and 4c, and will be checked by the attending physician.

c. Benefits and risks assessment, group relatedness

The maximum total amount of blood removed in a patient will be circa 50 ml per day or a maximum of 300 ml for 6 days (a minimum of 15 ml per day or 90 ml for 6 days is common after heart and lung transplantations) and an additional 2,5 ml after circa 1, 3 and 6 months. All patients are already equipped with an arterial line to draw blood samples which is equivalent in current daily practice. Concerning the urine collection, all patients are already equipped with a urine catheter to the current daily practice. Thus no supplementary pain will be suffered by introducing an arterial line or a urinary catheter. At 1, 3, and 6 month only one extra blood sample will be drawn via a venal puncture and urine will be collected for 24 hours by the patient. Patient's safety will increase due to a better insight in pharmacokinetics of tacrolimus shortly after transplantation.

d. Compensation for injury

The Investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The Investigator has an insurance which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of May 18th 2012). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as conductor in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

a. Handling and storage of data and documents

a.a. Recording of data

After informed consent for participation has been given, each participant will be given a Unique Trial Number. Subjects are only traceable by this number to the clinical

investigators. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

Data are encoded by the Unique Trial Number. All data will be recorded in the CRF. All missing data will be explained. CRF items not done will be marked as "ND". If an item is unknown or not applicable to the specified case, the space on the CRF will be marked "NA". Data that has been collected but cannot be retrieved will also be marked "NA". All data entries will be made in permanent, black ink. Entry errors will have a single line drawn through them with the correction entered above. All entry errors will be initialled and dated. The Investigator of this study is responsible according to ICH-GCP guidelines for assuring proper study conduct with regard to protocol adherence and validity of the data recorded on the CRFs.

The investigator has therefore assigned a qualified study monitor to this study. His duties are to assist the investigators in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitor will ensure that the investigator understands all applicable regulations concerning the clinical evaluation of an investigational drug, as laid down in ICH GCP guidelines.

The investigator agrees to allow the monitor direct access to the study drug dispensing and storage area and to all clinical data of the study subjects for the above purposes and agrees to assist the monitor in these activities. The investigator accepts that the monitor will visit the center at regular intervals, once per 3 months, to review and verify the data collected. The monitor will regard all information that is supplied to him or her as strictly confidential. Further information on monitoring the data can be found in the monitoring plan which is added to this study protocol.

a.b. Data management
Data will be entered into a database. All data will be entered by means of double entry verification. Queries will be issued, e.g. on missing data, inconsistencies, illegible data, illegal values and unclear corrected items.

a.c. Use of information
Clinical research personnel assigned by the Principal Investigator will require direct access to the subject's notes for source data verification. The confidentiality of all the subjects' identities will be maintained. Only the Unique Trial Number will be used on CRFs and in all study correspondence. No material bearing a subject's name will be kept on file by the clinical research personnel.

a.d. Record retention
The principal investigator will maintain a study file, which is used to file the protocol, correspondence with the independent ethics committee (IEC) and other study-related documents. The principal investigator's copy of the case report forms (CRF), study file, consent forms, and the subject identification list must be kept by the investigator for at least 20 years. Safety of the study will be checked by the safety monitor every month.

b. Amendments
Amendments are changes made to the research protocol after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

c. Annual progress report
The sponsor/ investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

d. End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's blood sampling. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/ abstracts of the study, to the accredited METC.

e. Public disclosure and publication policy
Results of the study will be made public in peer-reviewed scientific journals and at (scientific) symposia and congresses. The manufacturer of the study medication (Astellas) will have no influence on the content and/or presentation of the results of this study.

The authors of the publications derived directly from this study will be ordered as follows:
M.A. Sikma, MD
C.C. Hunault, MD, PhD
E.M. Van Maarseveen, PharmD
H.M. Koudijs, medical student
A.L. Van Dapperen, pharmaceutical student
Prof. J.R. Lahpor, MD, PhD
E.A. van de Graaf, MD, PhD
J.H. Kirkels, MD, PhD
Prof. M.C. Verhaar, MD, PhD
Prof. J.C. Grutters, MD, PhD
Prof. J. Kesecioglu, MD, PhD
Prof. J. Meulenbelt, MD, PhD

11. REFERENCE LIST

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16.1.2 Example case report form

Case Report Form
SPARTACUS study

Unique Trial Number: UTN.SPART.002

Protocol title	**A multi Centre, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Six Days after Transplantation** "SPARTACUS"
Protocol version	Version June, 2013

General instruction to complete the CRF	
Time format	The time has to be quoted in the 24 hour format, e.g. half past two p.m. has to be quoted as 14:30.

Check mark (☐):	Indicate the applicable check mark box ☐, by cross out ☒, or by check mark ☑
Written information	Write out all information in the indicated writing space (.....)
Value information	Make use of a preceding zero to prevent value misinterpretation, |0|2| instead of only |_|2|
Error rectification	Rectify an error by using a single strikethrough from the lower left to the upper right corner. Thereafter, place the correction nearby. |0|2| changed to ~~|0|2|~~ 20 **Initials** 2010/02/15 Always put initials and date next to the correction.

Inclusion criteria

- ☐ Patients ≥ 18 years
- ☐ Patients admitted to the ICC of UMCU after heart or lung transplantation
- ☐ Treated with tacrolimus (Prograft®; Astellas Pharma Europe)
- ☐ Informed consent obtained

Exclusion criteria

- ☐ Patients < 18 years
- ☐ Patients who die within one day after admission to the ICC of UMCU
- ☐ Withdrawal of informed consent
- ☐ Allergy towards tacrolimus or macrolides
- ☐ Patients on total parenteral nutrition

Check in date: |__|__|/|__|__|/|__|__|__|__|
Day Month Year

INFORMED CONSENT	
Informed consent form	
Completed appropriately and signed by volunteer?	Yes ☐ No ☐
Signed on date:	|__|__|/|__|__|/|__|__|__|__| day / month / year
Signed by clinical investigator?	Yes ☐ No ☐

Demographic Data	
♦ Gender	Female ☐ Male ☐
♦ Age	|__|__| yrs.
♦ Weight	|__|__|__|kg
♦ Lenght	|__|__|__|cm

Medical history	
Past medical history reports?	Yes * No
Heart failure or **Lung failure**	
Cystic Fibrosis or not	Yes No
Pre-existent renal dysfunction	Yes No

If **yes***, please specify!

Schemetime		Planned time	Procedure
Pre-study			• **Informed consent** • **Age** • **Gender** • **Weight** • **Height** • **Medical history** • **Indication of transplantation(heart or lung failure; cystic fibrosis or not)** • **Lung transplantation double or single?** • **Pre-existent renal dysfunction?**
Day 1	-12	06:00	• **Heart or Lung Transplantation day** • Blood sampling for measurement tacrolimus baseline+ Unbound concentration0 (1 ml of blood will be withdrawn for baseline measurement if patient starts with tacrolimus at 6 AM, before administration of oral dose tacrolimus) 0
	t=00:00	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration0 **1** • **Blood sampling CYP3a4/CYP3a5/Pgp** • **Blood sampling Biochemical/Heamatological** **(Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**
	1	19:00	Blood sampling for measurement tacrolimus I **2**
	1,5	19:30	Blood sampling for measurement tacrolimus II **3**
	2	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF **4**
	2,5	20:30	Blood sampling for measurement tacrolimus IV **5**
	3	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF **6**
	4	22:00	Blood sampling for measurement tacrolimus VI **7**
	6	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 **8** • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no

Day 2				
	8	02:00	Blood sampling for measurement tacrolimus VIII	9
	12	06:00	Blood sampling for measurement tacrolimus IX	10
	24	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration 0 • **Blood sampling Biochemical/Heamatological (Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**	11
	25	19:00	Blood sampling for measurement tacrolimus I	**12**
	25,5	19:30	Blood sampling for measurement tacrolimus II	**13**
	26	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF	**14**
	26,5	20:30	Blood sampling for measurement tacrolimus IV	**15**
	27	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF	**16**
	28	22:00	Blood sampling for measurement tacrolimus VI	**17**
	30	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no	**18**
Day 3	32	02:00	Blood sampling for measurement tacrolimus VIII	**19**
	36	06:00	Blood sampling for measurement tacrolimus IX	**20**
	38	08:00	• Blood sampling Sulfamethoxazol • Blood sampling Gangciclovir/Acyclovir/Tobramycine	**21**
	41	11:00	• Blood sampling Gangciclovir/Acyclovir/Tobramycine	**22**
	48	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration 0 • **Blood sampling Biochemical/Heamatological (Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**	23
	49	19:00	Blood sampling for measurement tacrolimus I	**24**
	49,5	19:30	Blood sampling for measurement tacrolimus II	**25**
	50	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF	**26**
	50,5	20:30	Blood sampling for measurement tacrolimus IV	**27**
	51	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF	**28**
	52	22:00	Blood sampling for measurement tacrolimus VI	**29**
	54	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no	**30**

Day 4				
	56	02:00	Blood sampling for measurement tacrolimus VIII	31
	60	06:00	Blood sampling for measurement tacrolimus IX	32
	72	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration 0 • **Blood sampling Biochemical/Heamatological (Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**	33
	73	19:00	Blood sampling for measurement tacrolimus I	34
	73,5	19:30	Blood sampling for measurement tacrolimus II	35
	74	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF	36
	74,5	20:30	Blood sampling for measurement tacrolimus IV	37
	75	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF	38
	76	22:00	Blood sampling for measurement tacrolimus VI	39
	78	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no	40
Day 5				
	80	02:00	Blood sampling for measurement tacrolimus VIII	41
	84	06:00	Blood sampling for measurement tacrolimus IX	42
	96	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration 0 • **Blood sampling Biochemical/Heamatological (Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**	43
	97	19:00	Blood sampling for measurement tacrolimus I	44
	97,5	19:30	Blood sampling for measurement tacrolimus II	45
	98	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF	46
	98,5	20:30	Blood sampling for measurement tacrolimus IV	47
	99	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF	48
	100	22:00	Blood sampling for measurement tacrolimus VI	49
	102	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no	50

Day 6	104	02:00	Blood sampling for measurement tacrolimus VIII	**51**
	108	06:00	Blood sampling for measurement tacrolimus IX	52
	110	08:00	• Blood sampling Sulfamethoxazol • Blood sampling Gangciclovir/Acyclovir/Tobramycine	**53**
	113	11:00	• Blood sampling Gangciclovir/Acyclovir/Tobramycine	**53**
	120	**18.00**	Blood sampling for measurement tacrolimus baseline+ Unbound concentration 0 • **Blood sampling Biochemical/Heamatological (Ureum; Creat; *ALAT;Bilirubine; CRP; Albumin;HDL/ Hb; Ht; Leuco+diff)*** • **Blood sampling: AGP** • **Blood sampling pH** • **Blood sampling serum** **Administration tacrolimus orally 0,1 mg/kg day**	**55**
	121	19:00	Blood sampling for measurement tacrolimus I	**56**
	121,5	19:30	Blood sampling for measurement tacrolimus II	**57**
	122	20:00	Blood sampling for measurement tacrolimus III+ Unbound concentration2 NON CF	**58**
	122,5	20:30	Blood sampling for measurement tacrolimus IV	**59**
	123	21:00	Blood sampling for measurement tacrolimus V+ Unbound concentration2 CF	**60**
	124	22:00	Blood sampling for measurement tacrolimus VI	**61**
	126	24:00	Blood sampling for measurement tacrolimus VII+ Unbound concentration6 • **24-hours urine collection** • **Renal replacement therapy: yes/no** • diarrhea: yes/no	**62**
	Day 7			
	128	02:00	Blood sampling for measurement tacrolimus VIII	**63**
	132	06:00	Blood sampling for measurement tacrolimus IX	64
Visit 1	1 month		• **Creatinine clearance 24 hours urine collection**	
Visit 2	3 month		• **Creatinine clearance 24 hours urine collection**	
Visit 3	6 month		• **Creatinine clearance 24 hours urine collection**	

DAY 1

date: |__|__|/|__|__|/|__|__|__|__|
Day Month Year

♦ **Planned Time: 18:00 hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

	Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin HDL/Hb; Ht; Leuco+diff)*	Sample drawn? Yes ☐ No* ☐
	pH	Sample drawn? Yes ☐ No* ☐
	AGP	Sample drawn? Yes ☐ No* ☐
	Extra tube EDTA 1ml	Sample drawn? Yes ☐ No* ☐
	CYP 3a4/CYP3a5/Pgp	Sample drawn? Yes ☐ No* ☐

1. Blood sample for measurement baseline tacrolimus **t=00:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day **time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**
Start 24-hour urine collection	Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 19:00 PM hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

2. Blood sample for measurement tacrolimus I **t=01:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 19:30 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

3. Blood sample for measurement tacrolimus II **t=01:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 20:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

4. Blood sample for measurement tacrolimus III **t=02:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	

*If **No**, please specify:

♦ **Planned Time: 20:30 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

5. Blood sample for measurement tacrolimus IV **t=02:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 21:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

6. Blood sample for measurement tacrolimus V **t=03:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 22:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

7. Blood sample for measurement tacrolimus VI **t=04:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 24:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

8. Blood sample for measurement tacrolimus VII **t=06:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn?

	10 ml EDTA (purple) tacrolimus unbound concentration	Yes ☐ No* ☐

*If No, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐
Renal Replacement Therapy?	Yes ☐ No ☐
Diarrhea?	Yes ☐ No ☐

*If No, please specify:

DAY 2

date: |__|__|/|__|__|/|__|__|__|__|
Day Month Year

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

9. Blood sample for measurement tacrolimus VIII **t=08:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

10. Blood sample for measurement tacrolimus IX **t=12:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐
Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

*If No, please specify:

♦ Planned Time: 18:00 hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

	Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin HDL/Hb; Ht; Leuco+diff)*	Sample drawn? Yes ☐ No* ☐
	pH	Sample drawn? Yes ☐ No* ☐
	AGP	Sample drawn? Yes ☐ No* ☐
	Extra tube EDTA 1ml	Sample drawn? Yes ☐ No* ☐

11. Blood sample for measurement baseline tacrolimus **t=24:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**
Start 24-hour urine collection		Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 19:00 PM hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

12. Blood sample for measurement tacrolimus I **t=25:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 19:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

13. Blood sample for measurement tacrolimus II **t=25:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 20:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

14. Blood sample for measurement tacrolimus III	t=26:00 hours
1 ml EDTA (pink) tacrolimus whole-blood 10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 20:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

15. Blood sample for measurement tacrolimus IV	t=26:30 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 21:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

16. Blood sample for measurement tacrolimus V	t=27:00 hours
1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 22:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

17. Blood sample for measurement tacrolimus VI	t=28:00 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 24:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

18. Blood sample for measurement tacrolimus VII	t=30:00 hours
1 ml EDTA (pink) tacrolimus whole-blood 10 ml EDTA (purple) tacrolimus unbound concentration	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐
Renal Replacement Therapy?	Yes ☐ No ☐
Diarrhea?	Yes ☐ No ☐

*If **No**, please specify:

DAY 3

date: |__|__|/|__|__|/|__|__|__|__| (Day Month Year)

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

19. Blood sample for measurement tacrolimus VIII **t=32:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

20. Blood sample for measurement tacrolimus IX **t=36:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐
Administration of Tacrolimus 0,1 mg/kg/day **time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

♦ **Planned Time: 08:00 hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

21. Blood sample for measurement **t=38:00 hours**

0,5 ml (pink) measurement Sulfamethoxazole *(if prescribed)*	Sample drawn? Yes ☐ No* ☐
1 ml EDTA (pink) measurement ganciclovir/Aciclovir/tobramycine *(if prescribed)*	

*If **No**, please specify:

♦ **Planned Time: 11:00 hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

22. Blood sample for measurement **t=41:00 hours**

	1 ml EDTA (pink) measurement ganciclovir/Aciclovir/tobramycine (*if prescribed)*	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 18:00 hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours
Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin HDL/Hb; Ht; Leuco+diff)*		Sample drawn? Yes ☐ No* ☐
pH		Sample drawn? Yes ☐ No* ☐
AGP		Sample drawn? Yes ☐ No* ☐
Extra tube EDTA 1ml		Sample drawn? Yes ☐ No* ☐

23. Blood sample for measurement baseline tacrolimus **t=48:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day	**time|__|__| : |__|__| hours**	**Dose:** |__|__|__| **mg**

*If No, please specify:

♦ Planned Time: 19:00 PM hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

24. Blood sample for measurement tacrolimus I **t=49:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 19:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

25. Blood sample for measurement tacrolimus II **t=49:30 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 20:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

26. Blood sample for measurement tacrolimus III **t=50:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn?

	10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 20:30 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

27. Blood sample for measurement tacrolimus IV **t=50:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 21:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

28. Blood sample for measurement tacrolimus V **t=51:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 22:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

29. Blood sample for measurement tacrolimus VI **t=52:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 24:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

30. Blood sample for measurement tacrolimus VII **t=54:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

*If **No**, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐
Renal Replacement Therapy?	Yes ☐ No* ☐
Diarrhea?	Yes ☐ No* ☐

*If **No**, please specify:

DAY 4

date: |__|__|/|__|__|/|__|__|__|__|
Day **Month** **Year**

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

31. Blood sample for measurement tacrolimus VIII **t=56:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

32. Blood sample for measurement tacrolimus IX **t=60:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐

Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

*If **No**, please specify:

♦ Planned Time: **18:00** hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

	Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin HDL/Hb; Ht; Leuco+diff)*	Sample drawn? Yes ☐ No* ☐
	pH	Sample drawn? Yes ☐ No* ☐
	AGP	Sample drawn? Yes ☐ No* ☐
	Extra tube EDTA 1ml	Sample drawn? Yes ☐ No* ☐

33. Blood sample for measurement baseline tacrolimus **t=72:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day time|__|__| : |__|__| hours	**Dose:** |__|__|__| mg

*If No, please specify:

♦ Planned Time: **19:00** PM hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

34. Blood sample for measurement tacrolimus I **t=73:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: **19:30** hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

35. Blood sample for measurement tacrolimus II **t=73:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: **20:00** hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

36. Blood sample for measurement tacrolimus III **t=74:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	

*If **No**, please specify:

♦ **Planned Time: 20:30 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

37. Blood sample for measurement tacrolimus IV **t=74:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 21:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

38. Blood sample for measurement tacrolimus V **t=75:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 22:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

39. Blood sample for measurement tacrolimus VI **t=76:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 24:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

40. Blood sample for measurement tacrolimus VII **t=78:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

*If **No**, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐
Renal Replacement Therapy?	Yes ☐ No ☐
Diarrhea?	Yes ☐ No ☐

*If **No**, please specify:

DAY 5

date: |__|__|/|__|__|/|__|__|__|__|
Day **Month** **Year**

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

41. Blood sample for measurement tacrolimus VIII **t=80:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

42. Blood sample for measurement tacrolimus IX **t=84:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐

Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

*If **No**, please specify:

♦ Planned Time: 18:00 hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

	Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin; HDL/Hb; Ht; Leuco+diff)*	Sample drawn? Yes ☐ No* ☐
	pH	Sample drawn? Yes ☐ No* ☐
	AGP	Sample drawn? Yes ☐ No* ☐
	Extra tube EDTA 1ml	Sample drawn? Yes ☐ No* ☐

43. Blood sample for measurement baseline tacrolimus **t=96:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day time|__|__| : |__|__| hours	**Dose:** |__|__|__| mg

*If **No**, please specify:

♦ Planned Time: 19:00 PM hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

44. Blood sample for measurement tacrolimus I **t=97:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 19:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

45. Blood sample for measurement tacrolimus II **t=97:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 20:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

46. Blood sample for measurement tacrolimus III **t=98:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn?

	10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 20:30 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

47. Blood sample for measurement tacrolimus IV **t=98:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 21:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

48. Blood sample for measurement tacrolimus V **t=99:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 22:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

49. Blood sample for measurement tacrolimus VI **t=100:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 24:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

50. Blood sample for measurement tacrolimus VII **t=102:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

*If **No**, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐

Renal Replacement Therapy?	Yes ☐ No* ☐
Diarrhea?	Yes ☐ No* ☐

*If **No**, please specify:

DAY 6

date: |__|__|/|__|__|/|__|__|__|__|
Day **Month** **Year**

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

51. Blood sample for measurement tacrolimus VIII **t=104:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

52. Blood sample for measurement tacrolimus IX **t=108:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐
Administration of Tacrolimus 0,1 mg/kg/day **time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

*If **No**, please specify:

♦ **Planned Time: 08:00 hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

53. Blood sample for measurement **t=110:00 hours**

0,5 ml (pink) measurement Sulfamethoxazole *(if prescribed)*	Sample drawn? Yes ☐ No* ☐
1 ml EDTA (pink) measurement ganciclovir/Aciclovir/tobramycine *(if prescribed)*	

*If **No**, please specify:

♦ **Planned Time: 11:00 hrs**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

54. **Blood sample for measurement**	**t=113:00 hours**
1 ml EDTA (pink) measurement ganciclovir/Aciclovir/tobramycine (*if prescribed)*	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 18:00 hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

	Biochemical/Heamatological parameters *(Ureum; Creat; ALAT; Bilirubine;CRP; Albumin HDL/Hb; Ht; Leuco+diff)*	Sample drawn? Yes ☐ No* ☐
	pH	Sample drawn? Yes ☐ No* ☐
	AGP	Sample drawn? Yes ☐ No* ☐
	Extra tube EDTA 1ml	Sample drawn? Yes ☐ No* ☐

55. Blood sample for measurement baseline tacrolimus **t=120:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
	10 ml EDTA (purple) tacrolimus unbound concentration	

Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**
Start 24-hour urine collection		Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 19:00 PM hrs	♦ Actual Recorded Time	|__|__| : |__|__| hours

56. Blood sample for measurement tacrolimus I **t=121:00 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 19:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

57. Blood sample for measurement tacrolimus II **t=121:30 hours**

	1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ Planned Time: 20:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

58. Blood sample for measurement tacrolimus III	t=122:00 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
10 ml EDTA (purple) tacrolimus unbound concentration (CF patient 21:00)	

*If No, please specify:

♦ Planned Time: 20:30 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

59. Blood sample for measurement tacrolimus IV	t=122:30 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 21:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

60. Blood sample for measurement tacrolimus V	t=123:00 hours
1 ml EDTA (pink) tacrolimus whole-blood (CF patient + Unbound concentration)	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 22:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

61. Blood sample for measurement tacrolimus VI	t=124:00 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If No, please specify:

♦ Planned Time: 24:00 hours	♦ Actual Recorded Time	|__|__| : |__|__| hours

62. Blood sample for measurement tacrolimus VII	t=126:00 hours
1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐
10 ml EDTA (purple) tacrolimus unbound concentration	

*If No, please specify:

Stop/Start 24-hour urine collection	Yes ☐ No* ☐
Renal Replacement Therapy?	Yes ☐ No* ☐
Diarrhea?	Yes ☐ No* ☐

*If **No**, please specify:

DAY 7

date: |__|__|/|__|__|/|__|__|__|__|
Day **Month** **Year**

♦ **Planned Time: 02:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

63. Blood sample for measurement tacrolimus VIII **t=128:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood	Sample drawn? Yes ☐ No* ☐

*If **No**, please specify:

♦ **Planned Time: 06:00 hours**	♦ **Actual Recorded Time**	|__|__| : |__|__| **hours**

64. Blood sample for measurement tacrolimus IX **t=132:00 hours**

1 ml EDTA (pink) tacrolimus whole-blood *regular blood sampling UMC Utrecht*	Sample drawn? Yes ☐ No* ☐

Administration of Tacrolimus 0,1 mg/kg/day	**time**|__|__| : |__|__| **hours**	**Dose:** |__|__|__| **mg**

*If **No**, please specify:

Visit 1	t= 1 month	date: |__|__|/|__|__|/|__|__|__|__| Day Month Year

24-hour urine collection	**Volume:**	|__|__|__| **ml**	Yes ☐	No* ☐
Renal Replacement therapy			Yes ☐	No ☐
Blood sample Ganciclovir/Aciclovir/Tobramycin Sulfamethoxazole			Yes ☐	No ☐

*If **No/**, please specify:

Visit 2	t= 3 month	date: |__|__|/|__|__|/|__|__|__|__| Day Month Year

24-hour urine collection	**Volume:**	|__|__|__| **ml**	Yes ☐	No* ☐
Renal Replacement therapy			Yes ☐	No ☐
Blood sample Ganciclovir/Aciclovir/Tobramycin Sulfamethoxazole			Yes ☐	No ☐

*If **No/**, please specify:

Visit 3	t= 6 month	date: __/__/____ Day Month Year

24-hour urine collection ***(regular measurement))***	**Volume:**	___ ml	Yes ☐	No* ☐
Renal Replacement therapy			Yes ☐	No ☐
Blood sample Ganciclovir/Aciclovir/Tobramycin Sulfamethoxazole			Yes ☐	No ☐
Organ Rejection? (EPD result biopsy)			Yes ☐	No* ☐

*If **No/**, please specify:

These events are often seen in heart and lung transplantation patients and are not due to blood sampling via an arterial catheter.
Due the observational nature of the study, these events will not be due to this study and therefore they will not be reported separately.
They will be recorded in the CRF and in the AEs recording and reporting log in the Master Trial File section 12

(S) Adverse Event	Date							
AE (*6 month reported*)								
Infections or haemorrhage from the arterial catheter								
SAE								
Death								
Prolongation of existing inpatients' hospitalisation or requiring hospitalisation								
Repaeted Surgery								
Significant disability or incapacity								
Wound Compilcations								
Serious bleeding (>1000 ml per day)								
Sepsis								
Multi organ Failure								
Prolonged mechanical ventilation (>1 day)								
Arrhythmias								
Pericardial tamponade								
Severe anaemia								
Disseminated intravasculair coagulation								
Severe electrolyte disturbances								
Disturbances of proteins								
Bowel Disturbances								
Weight loss								
Decubitus								
Encephalopathy or delirium								
Pericardial or pleural effusion and pain								

CHECK OUT

date: |__|__|/|__|__|/|__|__|__|__|
Day **Month** **Year**

	Study Completion	
	Did patient complete the study?	Yes ☐ No ☐
	Main reason for withdrawal (please give details) 5. Adverse Events; 6. Inter-current illness that, in the judgment of the Investigator, might invalidate the study or place the participant at risk; 7. At the request of the volunteer or principal Investigator, whether for administrative or other reasons; 8. Due to protocol violations or unreliable behaviour. If the reason for withdrawal of a subject from the study is an adverse event, the principal specific event and any related test results will be recorded in the CRF. When a subject is withdrawn from the study, all observations collected up to the time of termination will be recorded in the CRF along with the reason for termination	
	♦ Violation of inclusion criteria	Yes ☐ No ☐
	♦ Adverse event (including death)	Yes ☐ No ☐
	♦ Lost to follow-up	Yes ☐ No ☐
	♦ Withdrew consent	Yes ☐ No ☐
	♦ Protocol violation	Yes ☐ No ☐
	♦ Other	Yes ☐ No ☐
	Was the patient replaced	Yes ☐ No ☐

Clinical Investigator Certification

Herewith, I (specified name below) certify that I have reviewed the data filled out in these pages of this Case Report Form for this patient and found them to be complete and accurate.

Name: _____.

Signature: _____.

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms

Local regulatory authorities:
The accredited review board for human studies
University Medical Center Utrecht
Huispostnummer D 01.343
Postbus 85500
3508 GA UTRECHT
The Netherlands

Medical research Ethics Committees United
St. Antonius Hospital
Department St. Antonius Research & Development
Postbus 2500
3430 EM Nieuwegein
The Netherlands

Example of written patient information with sample consent form:

Universitair Medisch Centrum
Utrecht

Informatiebrief

Onderzoek naar de werking van het medicijn tacrolimus tijdens de eerste 6 dagen na hart- en longtransplantaties

(A Multi Centre, Prospective, Observational, Open-label, Pharmacokinetic Study of Tacrolimus in Heart and Lung Transplantation Patients during the First Days after Transplantation)

Versie: 5
Datum: 19/03/2013

Geachte heer, mevrouw,

U gaat in de toekomst mogelijk een hart- of longtransplantatie ondergaan. Daarbij zult u het medicijn tacrolimus gebruiken. Zoals u waarschijnlijk van uw behandelend arts hebt gehoord, doen wij medisch-wetenschappelijk onderzoek naar de gedragingen van dat geneesmiddel. Wij vragen u vriendelijk om mee te doen aan dit onderzoek (zie titel). U beslist zelf of u wilt meedoen. Voordat u de beslissing neemt, is het belangrijk om meer te weten over het onderzoek. Lees deze informatiebrief rustig door. Bespreek het met partner, vrienden of familie. Lees ook de Algemene brochure "Medisch-wetenschappelijk onderzoek. Algemene informatie voor de proefpersoon" uitgebracht door het ministerie van VWS. Daarin staat veel algemene informatie over medisch-wetenschappelijk onderzoek. Hebt u na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoeker. Op bladzijde 6 vindt u de contactgegevens. Ook staat daar een onafhankelijke persoon vermeld, die veel weet van het onderzoek. Aan deze persoon kunt u ook uw vragen stellen.

1. Inleiding en achtergrond
Jaarlijks worden in het UMC Utrecht ongeveer 30 hart- en longtransplantaties uitgevoerd. Dit zijn ingrijpende behandelingen, die pas sinds de jaren tachtig en negentig op wat grotere schaal worden toegepast.

Na de operatie verblijven transplantatiepatiënten gemiddeld drie tot zeven dagen op de Intensive Care afdeling. Ze worden hier intensief in de gaten gehouden en krijgen medicijnen toegediend om te voorkomen, dat het afweersysteem het donororgaan afstoot. Om een afstotingsreactie te voorkomen wordt onder andere het medicijn tacrolimus gegeven, wat de werking van het afweersysteem onderdrukt. Het is sinds 1993 op de markt onder de merknaam Prograft®.

Tijdens de eerste dagen na de operatie blijkt het lastig om tacrolimus goed te doseren. Dat is belangrijk, want bij een te hoge bloedconcentratie van het medicijn, kunnen er bijwerkingen optreden, en bij een te lage bloedconcentratie bestaat er kans op afstoting van het

getransplanteerde orgaan. In de praktijk blijken deze bloedconcentraties zeer veranderlijk en lastig te voorspellen. Voor elke patiënt zijn daarom individuele aanpassingen in de dosering nodig. Op dit moment weten we nog maar weinig over de factoren die van invloed zijn op deze wisselingen in de bloedconcentraties bij het toedienen van tacrolimus kort na operaties.
Om in de toekomst het medicijn tacrolimus beter en veiliger te kunnen doseren bij transplantaties vragen wij u om mee te werken aan een onderzoek op de intensive care in de eerste dagen na uw transplantatieoperatie.

2. Doel van het onderzoek
Het doel van dit onderzoek is een beter inzicht te krijgen in de verwerking van de toegediende stof tacrolimus door het lichaam tijdens de eerste dagen na transplantatie. Zo kunnen we afstoting van het getransplanteerde orgaan of bijwerkingen van het medicijn helpen te voorkomen. Daarnaast wordt in dit onderzoek gekeken of veranderingen in het aantal rode bloedcellen of eiwitten in het bloed of de hoeveelheid toegediend vocht veranderingen in de bloedconcentratie van tacrolimus teweegbrengen. Eveneens wordt gekeken of veranderingen in nierfunctie, leverfunctie of het hebben van diarree van invloed zijn op de bloedconcentratie van tacrolimus. Ook wordt er in dit onderzoek gekeken of medicijnen en genetische factoren, die het omzetten van het medicijn in niet actieve stoffen beïnvloeden, de bloedconcentraties van tacrolimus kunnen veranderen. De uitkomsten van dit onderzoek kunnen van nut zijn om in de toekomst het medicijn beter en veiliger te kunnen doseren, op iedere patiënt afzonderlijk afgestemd, tijdens het verblijf op de intensive care afdeling in de eerste dagen na de transplantatie.

3. Uitvoering van het onderzoek
Tijdens het onderzoek zult u de gebruikelijke behandeling en zorg ontvangen. Geheel volgens de standaard procedures en behandeling zult u via de mond of via een sonde tweemaal daags het medicijn tacrolimus toegediend krijgen. Vervolgens zal op vastgestelde tijdstippen (direct voor inname, ½, 1, 1½, 2, 2½, 3, 4, 6, 8 en 12 uur na inname) een kleine hoeveelheid bloed afgenomen worden via een catheter. Deze catheter wordt al bij de operatie standaard ingebracht. Ook worden er 's avonds voor inname van tacrolimus vier extra buisjes bloed afgenomen. Daarnaast wordt gedurende het onderzoek alle urine opgevangen door middel van een urinecatheter die al ingebracht is. Dit is ook een standaard procedure.

In het kader van het onderzoek worden een aantal extra gegevens vastgelegd over uw conditie, uw behandeling en het eventuele optreden van complicaties of bijwerkingen tijdens uw verblijf op de intensive care afdeling.

4. Omvang en duur van het onderzoek
Aan dit onderzoek zullen ongeveer 30 patiënten deelnemen. Het onderzoek start direct na de operatie. De bloedafnames en urineverzameling zullen de eerste 6 dagen na transplantatie, zolang u op de intensive care ligt, verricht worden. Na 1, 3 en 6 maanden, op het moment dat u ook naar poliklinische controles komt, vragen wij u nogmaals 24 uurs urine te verzamelen en eventueel nog 2,5 ml bloed extra af te staan.

5. Risico's en bijwerkingen
Elke patiënt krijgt tweemaal daags het medicijn toegediend via de mond of via een sonde. Na toediening zal op vastgestelde tijdstippen extra bloed afgenomen worden via een van de catheters die standaard worden ingebracht. Wanneer u 6 dagen of langer op de intensive care verblijft, staat u in totaal circa 300 ml bloed af. Dat kan een extra belasting vormen. Wanneer u korter op de intensive care verblijft zal er minder bloed afgenomen worden, ca 50 ml per dag.

Alle hart- en longtransplantatiepatiënten krijgen in de eerste dagen na de operatie tacrolimus toegediend. De belangrijkste bijwerkingen die bij het gebruik van het medicijn tacrolimus soms optreden zijn maagdarmklachten (misselijkheid, braken, diarree en buikpijn), nierbeschadigingen, verhoogde bloeddruk, verhoogde kans op ontstekingen, hoofdpijn, wazig zien, duizeligheid,

trillende of bevende handen, bloedarmoede of een verhoogd glucose- of kaliumgehalte van het bloed.

6. Hoe verloopt het onderzoek voor de deelnemer?
Tijdens het onderzoek krijgt u de gebruikelijke medicatie toegediend volgens het standaard behandelprotocol voor transplantatiepatiënten. Uw behandelend arts zal indien noodzakelijk uw dosering tacrolimus aanpassen volgens de standaard gebruikte methode. Deze arts is tijdens het onderzoek niet op de hoogte van de uitslagen van het, in het kader van het onderzoek, afgenomen bloed. De bloedafnames worden uitgevoerd door intensive care- of onderzoeksverpleegkundigen. Aangezien u de gebruikelijke behandeling en zorg zult ontvangen, zijn er geen beperkingen voor u als deelnemer en zijn er geen gevolgen voor het gebruik van eigen medicatie.

7. Wat zijn mogelijke voor- en nadelen van deelname aan dit onderzoek?
Er zijn voor u geen directe voordelen aan dit onderzoek. De uitkomst van het onderzoek zal niet direct op u van toepassing zijn. Als u deelneemt aan het onderzoek staat u, circa 50 ml extra bloed per dag af tijdens het verblijf op de intensive care. Aangezien u al intensief wordt bewaakt en verschillende slangetjes in de bloedbaan heeft, merkt u niets van de afname van dit bloed. Na 1, 3 en 6 maanden, bij één van uw poliklinische bezoeken, vragen wij u zo nodig nog eens 2,5 ml bloed af te staan en om 24-uurs urine te sparen. De uitkomsten van het onderzoek worden gebruikt om in de toekomst het medicijn

beter en veiliger te kunnen doseren, zodat ongewenste effecten van het medicijn zoveel mogelijk beperkt worden.

Voordeel: Doordat dit onderzoek zo compleet is, zal het van substantiële waarde zijn voor transplantatie patiënten. Met de kennis die verkregen zal worden met deze studie zal de tacrolimus bij hart- en longtransplantatie beter gedoseerd kunnen worden. De studie zal resulteren in minder bijwerkingen en minder toxische effecten en daardoor een toename van de patiëntenveiligheid.

8. Afronding
De resultaten van het onderzoek zullen worden gebruikt om het doseren van het medicijn tacrolimus te optimaliseren in de eerste dagen na een transplantatie. Na afronding van het onderzoek kunnen de algemene resultaten van het onderzoek aan u bekend worden gemaakt. Indien u dit wenst, kunt u dit aan ons kenbaar maken en zullen wij ervoor zorgen dat u hiervan op de hoogte wordt gesteld.

9. Kosten en vergoedingen
Aan deelname voor het onderzoek zijn geen kosten of vergoedingen verbonden. De onderzoekers ontvangen geen financiële steun van een bedrijf.

10. Vertrouwelijkheid
Derden kunnen tot uw persoon herleidbare onderzoeksgegevens alleen inzien met uw toestemming (aan te geven op het toestemmingsformulier). Als u instemt met deelname geeft u tegelijk toestemming tot vertrouwelijke inzage in uw medische gegevens door vertegenwoordigers van overheidsinstanties die daartoe bevoegd zijn, zoals de Inspectie voor de Gezondheidszorg of leden van de Medisch Ethische Toetsingscommissie, de auditor en de kwaliteitsmonitor. Zij zullen de kwaliteit van het onderzoek volgen en bewaken, door bijvoorbeeld onderzoeksgegevens te vergelijken met gegevens in uw medisch dossier. Als u instemt met deelname geeft u tegelijk toestemming tot deze vertrouwelijke inzage in uw medische gegevens. Onderzoeksgegevens worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens en het privacyreglement van het UMC Utrecht.

Persoonsgegevens die tijdens deze studie worden verzameld, worden vervangen door een codenummer. Alleen dat nummer wordt gebruikt voor studiedocumentatie, in rapporten of publicaties over dit onderzoek.

Slechts degene, die de sleutel van de code heeft (de onderzoeker) weet wie de persoon achter het codenummer is. De gegevens worden bewaard gedurende 20 jaar.

Lichaamsmaterialen die tijdens deze studie worden verzameld, worden gecodeerd en dus tot de persoon herleidbaar opgeslagen. Na afloop van de studie worden de opgeslagen lichaamsmaterialen gedurende maximaal 5 jaar bewaard. Het opgeslagen lichaamsmateriaal kan dan eventueel in de toekomst worden

gebruikt voor onderzoek met een zelfde onderzoeksdoel. Als u dat niet wilt, respecteren we dat vanzelfsprekend. U kunt uw weigering op het toestemmingsformulier schriftelijk vastleggen. Als u daar geen bezwaar tegen heeft, kunt u dat ook op het toestemmingsformulier aangeven. Wij zullen u,
wanneer dat andere onderzoek uitgevoerd zal gaan worden, daarover informeren. U kunt dan alsnog aangeven of uw gegevens daar wel of niet voor mogen worden gebruikt. We benaderen u pas nadat de medisch-ethische toetsingscommissie die dit onderzoek goedkeurde ook dat andere onderzoek heeft goedgekeurd.

Voor dit onderzoek is goedkeuring verkregen van de Raad van Bestuur na een positief oordeel van de Medisch Ethische Toetsingscommissie UMC Utrecht. De voor dit onderzoek geldende internationale richtlijnen worden nauwkeurig in acht genomen.

11. Vrijwillige deelname
Deelname aan dit onderzoek is geheel vrijwillig. Als u niet wilt deelnemen, hoeft u daarvoor geen reden te geven. Als u besluit niet mee te doen, geeft dat geen enkele verandering in uw verdere behandeling of begeleiding. Ook als u nu toestemming geeft, kunt u die altijd, ook tijdens het onderzoek, zonder opgave van redenen weer intrekken. Het onderzoek zal zo nauwkeurig mogelijk volgens plan verlopen. Als uw veiligheid of welbevinden in gevaar zijn, beëindigt de onderzoeker uw deelname aan het wetenschappelijk onderzoek direct.

12. Verzekering
Het UMC Utrecht heeft, als verrichter van dit onderzoek, een risicoverzekering afgesloten voor proefpersonen die meedoen aan wetenschappelijk onderzoek. Deze verzekering dekt schade door letsel of overlijden als gevolg van deelname aan het onderzoek, die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade moet zich hebben geopenbaard wanneer deze bij de verzekeraar is gemeld. Als u van mening bent dat u door of tijdens het onderzoek schade hebt opgelopen, adviseren wij u zo snel mogelijk contact op te nemen met de hieronder genoemde verzekeraar of schaderegelaar. U dient in dat geval de verzekeraar of schaderegelaar alle benodigde informatie te verschaffen. Het niet nakomen van deze verplichtingen kan leiden tot het niet vergoeden van de schade. Voor meer informatie over de verzekering verwijs ik u naar de bijlage behorend bij deze brief.

De verzekeraar van het onderzoek is:

Naam: Marketform Ltd
Adres: 8, Lloyd's Avenue, London EC3N 3EL, Groot-Brittannië

In geval van schade kunt u contact op nemen met de schaderegelaar:
Naam: Van Lanschot Assurantiën

T.a.v. dhr R. van Harten
Adres: Postbus 1999
5200 BZ 's-Hertogenbosch
Telefoon: 073-6924762
Email: r.vanharten@vanlanschotchabot.com

13. Wilt u nog iets weten?
Drs. M.A. Sikma, internist-intensivist, Intensive Care Centrum
en Nationaal Vergiftigingen Informatie Centrum (NVIC), UMC Utrecht

Prof. dr. J. Meulenbelt, internist-intensivist-toxicoloog, Intensive Care Centrum

en Nationaal Vergiftigingen Informatie Centrum (NVIC), UMC Utrecht

Dr.C.C. Hunault, arts-onderzoeker en klinisch epidemioloog

Nationaal Vergiftigingen Informatie Centrum (NVIC), UMC Utrecht

Mw. I.S. Van den Hengel-Koot, onderzoeksverpleegkundige
Nationaal Vergiftigingen Informatie Centrum (NVIC), UMC Utrecht

Adres NVIC:
UMCU afdeling Nationaal Vergiftigingen Informatie Centrum
Heidelberglaan 100
3584 CX Utrecht
Postadres: Huispostnummer B.00.118
Tel: 088-755 8561

*Als u twijfelt over deelname kunt u een **onafhankelijke arts** raadplegen, die zelf niet bij het onderzoek betrokken is, maar die wel deskundig is op het gebied van dit onderzoek en de behandeling na hart- of longtransplantaties. Ook als u voor of tijdens de studie vragen heeft die u liever niet aan de onderzoekers stelt, kunt u contact opnemen met de onafhankelijke arts. De onafhankelijk arts is dhr. Dr. D.W. De Lange, internist-intensivist/ infectioloog, UMC Utrecht, tel: 088-7553261.*

Indien u gedurende het onderzoek vragen heeft, kunt u ons tijdens kantooruren op bovenstaande telefoonnummers bereiken. Bij **noodgevallen** kunt u bellen naar 030-2748888 (24 uur per dag bereikbaar).

Hoe te handelen bij klachten?
Als u klachten heeft over het onderzoek, kunt u dit melden aan de onderzoeker of uw behandelend arts. Wilt u dit liever niet, dan kunt u contact opnemen met de Patiëntenservice.

Patiëntenservice is te vinden in de centrale hal van locatie AZU, naast de centrale opnamebalie, tel. 088-75 588 50.

14. Ondertekening toestemmingsformulier
Als u toestemt in deelname aan het onderzoek dient u een toestemmingsverklaring te dateren en te ondertekenen. U zult een kopie van de toestemmingsverklaring ontvangen.
- Wilsbekwame personen vanaf 18 jaar: ondertekening door deelnemer zelf *(Toestemmingsformulier A)*
- Wilsonbekwame personen vanaf 18 jaar: ondertekening door wettelijke vertegenwoordiger *(Toestemmingsformulier B)*

Met vriendelijke groet,

Drs. M.A. Sikma, internist-intensivist, Intensive Care Centrum
en NVIC, UMC Utrecht

Universitair Medisch Centrum
Utrecht

Toestemmingsformulier A (voor wilsbekwame volwassenen)

Pharmacokinetics of Tacrolimus in heart and lung transplantation patients
(Farmacokinetiek van het medicijn Tacrolimus bij hart- en longtransplantatie patiënten)

Ik bevestig dat ik het informatieformulier voor de proefpersoon (versie 3: 2012/09/25) heb gelezen. Ik heb de gelegenheid gehad om aanvullende vragen te stellen. Deze vragen zijn in voldoende mate beantwoord. Ik heb voldoende tijd gehad om over deelname na te denken.

Ik weet dat mijn deelname geheel vrijwillig is en dat ik mijn toestemming op ieder moment kan intrekken zonder dat ik daarvoor een reden hoef te geven.

Ik geef toestemming, dat auditors, medewerkers van de Inspectie voor de Gezondheidszorg, leden van de medisch-ethische toetsingscommissie of monitor inzage kunnen krijgen in mijn medische gegevens en onderzoeksgegevens.

Ik geef toestemming om de gegevens te verwerken voor de doeleinden zoals beschreven in de informatiebrief en daarnaast gedurende 20 jaar te bewaren en te gebruiken voor eventueel vervolg onderzoek zoals beschreven op bladzijde 5 punt 10.

Ik geef toestemming om onderzoek alleen gericht op genetische factoren die van invloed kunnen zijn op de bloedconcentraties van tacrolimus.

Ik geef wel/geen* toestemming om lichaamsmateriaal in de toekomst eventueel te gebruiken voor onderzoek met een zelfde onderzoeksdoel.

Ik stem in met mijn deelname aan bovengenoemd onderzoek.

Ik wil na het onderzoek wel/ niet algemene informatie ontvangen over de uitkomsten van dit onderzoek.

Naam proefpersoon:

Handtekening: Datum : __ / __ /

—

Ik heb mondelinge en schriftelijke toelichting verstrekt op het onderzoek. Ik verklaar mij bereid nog opkomende vragen over het onderzoek naar vermogen te beantwoorden. Een eventuele voortijdige beëindiging van deelname aan dit onderzoek zal niet van invloed zijn op de behandeling.

Naam onderzoeker:

Handtekening: Datum : __ / __ /

—

*** Doorhalen wat niet van toepassing is.**

(De proefpersoon ontvangt een ondertekende kopie van de Proefpersoneninformatie en het Toestemmingsformulier, het origineel blijft in het onderzoeksdossier van de onderzoeksarts).

Proefpersonenverzekering

Geachte heer, mevrouw,

U denkt er over na om mee te doen aan een wetenschappelijk onderzoek waaraan in meer of mindere mate risico's verbonden zijn. In verband met de Wet Medisch wetenschappelijk Onderzoek met mensen treft u hierbij aanvullende informatie aan betreffende de verzekering die in verband met de studie ten behoeve van alle proefpersonen is afgesloten.

Het UMC Utrecht heeft, als verrichter van dit onderzoek, een risicoverzekering afgesloten voor proefpersonen die meedoen aan wetenschappelijk onderzoek. De verzekering is afgesloten bij Marketform Limited te Londen onder het polisnummer L120082.

Deze verzekering dekt schade door dood of letsel die het gevolg is van deelname aan het onderzoek, en die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade wordt geacht zich te hebben geopenbaard wanneer deze bij de verzekeraar is gemeld.

De verzekeraar van het onderzoek is:
Naam: Marketform Ltd
Adres: 8, Lloyd's Avenue, London EC3N 3EL, Engeland.

In geval van schade kunt u contact op nemen met de schaderegelaar:

Naam: Van Lanschot Assurantien
T.a.v.dhr R. van Harten
Adres: Postbus 1999
5200 BZ 's-Hertogenbosch
Telefoon: 073-6924762
Email: r.vanharten@vanlanschotchabot.com

De verzekering biedt een maximum dekking van € 450.000 per proefpersoon en € 3.500.000 voor het gehele onderzoek, en € 5.000.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever. De dekking van specifieke schades en kosten is verder tot bepaalde bedragen beperkt. Dit is opgenomen in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Informatie hierover kunt u vinden op de website van de Centrale Commissie Mensgebonden Onderzoek: www.ccmo.nl.

Voor deze verzekering geldt een aantal uitsluitingen. De verzekering dekt niet:
- schade waarvan op grond van de aard van het onderzoek zeker of nagenoeg zeker was dat deze zich zou voordoen;
- schade aan de gezondheid die ook zou zijn ontstaan indien u niet aan het onderzoek had deelgenomen;
- schade die het gevolg is van het niet of niet volledig nakomen van aanwijzingen of instructies;
- schade aan nakomelingen, als gevolg van een nadelige inwerking van het onderzoek op u of uw nakomeling;
- bij onderzoek naar bestaande behandelmethoden: schade die het gevolg is van één van deze behandelmethoden;
- bij onderzoek naar de behandeling van specifieke gezondheidsproblemen: schade die het gevolg is van het niet verbeteren of van het verslechteren van deze gezondheidsproblemen.

16.1.4 Monitoring Plan

1.1 Algemeen

GCP 5.18.1

Het doel van monitoring van klinisch onderzoek is om te controleren of:

a. De rechten en het welzijn van de proefpersoon worden beschermd.
b. De gegevens uit het onderzoek die worden gerapporteerd juist en volledig verifieerbaar zijn in brondocumenten.
c. De uitvoering van het onderzoek in overeenstemming is met het/de op dat moment goedgekeurde protocol/amendement(en), met GCP en met de relevante wettelijke vereisten.

Het controleren of de gegevens uit het onderzoek juist worden gerapporteerd en volledig verifieerbaar zijn valt onder de monitoring en wordt 'Source Data Verification' (SDV) genoemd. Hierbij verifieert de monitor of de brongegevens uit bv. de status overeenkomen met de data in het Case Report Form (CRF).
Good Clinical Practice (GCP 5.18.1) schrijft voor dat de verrichter (=sponsor of the study) van een onderzoek een 'adequate mate en aard van' monitoring moet regelen.

Naar aanleiding van het NFU-advies (juni 2010; 'Kwaliteitsborging van Mensgebonden Onderzoek) is *on-site* monitoring van toepassing voor al het WMO-plichtig onderzoek (geneesmiddelen en niet geneesmiddelenonderzoek) in het UMC Utrecht en wordt afgestemd op de mate van risico. Dit betreft het toegevoegde risico van het onderzoek ten opzichte van de standaardbehandeling.
De afweging voor de mate van het risico en de daaraan gekoppelde monitoring is de verantwoordelijkheid van de verrichter en moet vooraf worden vastgelegd in een monitoringplan en is onderdeel van het onderzoek dossier.

1.2 Monitoringplan

In het protocol beoordeelde de verrichter het risico van dit onderzoek als: "**(Minimale overschrijding van) Verwaarloosbaar risico[1]**". Dit betekent dat minimale monitoring vereist is.

Uitvoer van monitoring

Monitoring zal uitgevoerd worden door een onafhankelijke monitor van het Nationaal Vergiftigingen Informatie Centrum: de QA-functionaris G.A. van Zoelen MSc of zijn vervanger.

Frequentie van de monitoring

Er zal minimaal een visit gepland worden per jaar. Verder zal er voorafgaand aan de studie een "initiatie visite" en aan het einde van de studie een "close-out visite" gepland worden.

Source Data Verification

- 100% controle op aanwezigheid en juistheid van de ingevulde Informed Consent (IC) formulieren
-100% controle op in- en exclusiecriteria
-10% van alle onderzoeksgegevens zullen gecontroleerd worden met de brondocumenten
NB: In het protocol en in het crf worden de variabelen weergegeven. Het primaire eindpunt is de concentratie tacrolimus in het bloed.
- 100% verificatie geëigende meldingsprocedure van gemelde SAEs en SUSARs
- 10% van de proefpersonen worden gecontroleerd op eventuele gemiste SAEs en SUSARs

Algemene controle
- Per monitorbezoek zal de inclusiesnelheid en het uitvalpercentage worden gerapporteerd.
- De aanwezigheid en volledigheid van de Trial Master File zal worden gecontroleerd.
- Er zal worden gecontroleerd of er studieprocedures aanwezig zijn en SOP's en of deze worden nageleefd en of het studiepersoneel hierop getraind is.
- Er zal gecontroleerd worden of de laboratoria en/of apotheek GLP/GMP gecertificeerd zijn. *(indien van toepassing))*
- Er zal gecontroleerd worden of apparatuur en faciliteiten voldoen aan de benodigde kwaliteitseisen. *(indien van toepassing)*

Rapportage
De monitor zal een schriftelijk verslag bij de verrichter (opdrachtgever) indienen na ieder bezoek aan een de onderzoekslocatie. Deze verslaglegging moet door de verrichter bewaard worden en bij een audit ter inzage beschikbaar zijn. Een onderzoekslocatie ontvangt altijd van ieder bezoek schriftelijk een samenvatting van de controles die er hebben plaatsgevonden en van de bevindingen.
Het "monitor visite rapport" (verslag n.a.v. het monitorbezoek) bevat:
- Een samenvatting van hetgeen de monitor heeft beoordeeld
- Een algemene beschrijving van de kwaliteit
- Een opsomming van belangrijke bevindingen/feiten, afwijkingen en tekortkomingen
- Een overzicht met te nemen maatregelen en aanbevelingen om naleving van het protocol te garanderen
- De "overall" conclusie

De verrichter (origineel) ontvangt ook het initiatie visite rapport en het close-out visite rapport. Indien van toepassing zullen ook overige relevante contacten betreffende het onderzoek schriftelijk vastgelegd worden.

16.1.5 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

The coordinating investigator, principal investigator, independent investigator, research nurse and monitor are all GCP/BROK accredited and have extensive experience in clinical pharmacology or clinical pharmacological studies.

Coordinating investigator/project leader:
Prof. J. Meulenbelt, MD, PhD died in December 2015
Head of department of National Poisons Information Center
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Resume of Prof. Jan Meulenbelt MD PhD:

CURRICULUM VITAE
Prof. Jan Meulenbelt MD,PhD, FAACT, FEAPCCT, internist, intensivist, toxicologist
Professor of Clinical Toxicology
Director National Poisons Information Center
Division of Anesthesiology, Intensive Care and Emergency Medicine,
University Medical Center Utrecht

1971 Diploma high school
1971-1973 Military service
1981-2015 Registered as physician
1986-2015 Registered as internist (re-registration every 5 years, last re-registration 2009)
1986-1989 Appointed as staff member internist at the National Poisons Information Centre of the National Institute for Public Health and the Environment, Bilthoven, The Netherlands
1986-2005 Appointed as Senior staff member internist of the Internal Medicine Intensive Care Department, Utrecht Medical Center Utrecht, Utrecht University, The Netherlands
1989-1996 Deputy head of the Internal Medicine Intensive Care, Department, Utrecht Medical Center Utrecht, Utrecht University, The Netherlands
1986-1998 Supervision of the emergency admission of groups of patients with chemical exposure at the Emergency Hospital of the Ministry of Defense at the Utrecht Medical Center Utrecht, Utrecht University, The Netherlands
1989-2015 Director of the National Poisons Information Centre of the National Institute for Public Health and the Environment, Bilthoven, The Netherlands

1990-1997 Member of the panel of experts on improving the prevention and treatment of acute human poisoning, EU Commission Directorate General Employment, Industrial Relations and Social Affairs, Health and Safety Directorate, Luxemburg
1993-1999 Deputy head National Centre for Medical Toxicology and Emergency Medicine; WHO Collaborating Centre on the Health Aspects of Chemical Accidents, Utrecht, The Netherlands
1993-2015 Besides being registered as internist also registered as intensivist (reregistration every 5 years, last re-registration 2010)
1994 PhD Thesis, Utrecht University, Utrecht, The Netherlands
1994-2015 Besides being registered as internist and intensivist, also registered as toxicologist (re-registration every 5 years, last re-registration 2009)
1994-1996 Specialist member of the Governing Body of the European Association of Poisons Centres and Clinical Toxicologists
1996-2015 Adviser for the Ministry of Health on clinical toxicological health effects forthcoming from smoke exposure of the Hercules airplane crash, Eindhoven, The Netherlands
1996-2000 General Secretary of the European Association of Poisons Centres and Clinical Toxicologists
1998-2015 Certified as Eurotox registered toxicologist
1998 Adviser for the Ministry of Health on clinical toxicological health effects forthcoming from smoke exposure from the EL AL-Boeing crash in Amsterdam, The Netherlands
2000-2002 President-elect of the European Association of Poisons Centres and Clinical Toxicologists
2000-2002 Chairman Scientific Committee of the European Association of Poisons Centres and Clinical Toxicologists
2000-2004 Responsible for the education program provided by the department of Acute Internal Medicine Care and Infectious diseases, Utrecht Medical Center Utrecht, Utrecht University, The Netherlands
2000-2005 International Workgroup of the EAPCCT (European Association of Poisons Centres and Clinical Toxicologists) and AACT (American Academy of Clinical Toxicologist) on position papers concerning the treatment of the poisoned patients
2000-2006 Clinical toxicological adviser concerning the health effects forthcoming from the smoke of the firework disaster Enschede, The Netherlands
2002-2004 President of the European Association of Poisons Centres and Clinical Toxicologists
2002-2015 My research unit achieved the official status (accreditation) for performing human studies under Good Clinical Practice
2004-2006 Past-President of the European Association of Poisons Centres and Clinical Toxicologists
2005-2015 Appointed as senior staff member (internist-intensivist-toxicologist) at the Division Intensive Care Centre, Utrecht Medical Center Utrecht, Utrecht University, The Netherlands
2006 Louis Roche Lecture 2006, EAPCCT (European Association of Poisons Centres and Clinical Toxicologists) Congress, Prague (19-22 April 2006), Czech Republic
2007-2015 Appointed full professor of Clinical Toxicology, Utrecht University, Utrecht, The Netherlands.
2008 Clinical Toxicological Advisor for the National Council for the Judiciary in a particular court case which had much impact on a National level. (The Council acts as a spokesperson for the Judiciary organization at both national and international levels and fulfils tasks in the area of international cooperation).
2008 7 July 2008, Inaugural speech as full professor at the Utrecht University, Utrecht, The Netherlands.
2009-2015 Appointed as member of the Health Council of The Netherlands of the Ministry of Health
2009-2015 Appointed as member of the Concilium Toxicologicum of the Dutch Society of Toxicology
2010-2015 Appointed as Fellow of the American Academy of Clinical Toxicology (AACT). Fellowship is provided to persons who have a relevant contribution to clinical toxicology by research (as evidenced by published papers relating to Clinical Toxicology) and to

educational activities concerning Clinical Toxicology. Furthermore,the fellow should have contributed significantly to the work of AACT and to the sponsored journal Clinical Toxicology.
2010-2014 Appointed as Chairman of Scientific Advisory Board of Netherlands Pharmacovigilance Centre, Lareb
2011 BROK registration [course; legislation and organization for clinical researchers] (reregistration 2015)
2014-2015 Appointed as Fellow of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). Fellowship is provided to persons who have a relevant contribution to clinical toxicology or poisons centre activity by research (as evidenced by published papers relating to Clinical Toxicology and/or to the work of poisons centres) and to educational activities concerning Clinical Toxicology. Furthermore, the fellow should have contributed significantly to the work of EAPCCT and to the sponsored journal Clinical Toxicology.

Commissions:
Member of the Medical Committee of the annual published book on Chemical Compound Monographs (1990-1996)
Member of the Commission Medical Technical Aspects of Chemical Disasters, Ministry of Health (1992-1995)
Member of the Commission Technical Aspects of Medical Triage in cases of Chemical Disasters, Ministry of Health (1993-1995)
Member (as Clinical Toxicological adviser) WHO-commission, to evaluate the cause and health impact of the metro-disaster 29 October 1995 Baku, Azerbaijan. "Report on the Accident in the Baku Subway" 2-9 november 1995.
Member (as representative of the Dutch Society of Toxicology) of the Project Group 'Erecting a National Institute for Emergency Medicine, Ministry of Health (1996-1997)
Member of the Project Group 'Improving the medical relief program in cases of incidents and disasters, Ministry of Inner Affairs and Ministry of Health (1996-1999)
Member of the Project Group 'Quality improving of the registration and triage of injured persons in cases of Incidents and Disasters, Ministry of Inner Affairs and Ministry of Health (1997- 1998)
Member of BOT-MI (Policy Team concerning the relief of Environmental Pollutions Incidents) Ministry of Housing, Spatial planning, and the Environment (1996-2015)
Member of the Scientific Advisory Board, Lareb (Netherlands Pharmacovigilance Foundation) (1997-2008)
Member of the National Team for Assessment and Monitoring of new drugs, Health Care Inspectorate, Ministry of Health (1998-2005)
Member of TIG (= Technical Information Group) of the National Network on Nuclear Incidents, participating ministries are: Ministry of Inner Affairs; Ministry of Health; Ministry of Housing, Spatial Planning, and the Environment; Ministry of Agriculture, Nature and Food quality; Ministry of Transport, Public works, and Water management; Ministry for Social Affairs and Employment (1999-2003)
Member of EPA-n (Unit Planning and Advice concerning nuclear incidents) participating ministries are: Ministry of Inner Affairs; Ministry of Health; Ministry of Housing, Spatial planning, and the Environment; Ministry of Agriculture, Nature and Food quality; Ministry of Transport,Public works, Water management; Ministry for Social Affairs and Employment (2003-2015)
National project group of the Dutch Society of Hospital Pharmacists concerning protocols on the treatment of intoxicated patients (2000-2015)
Member of the Commission "Exploration of the knowledge infrastructure on dangerous compounds in The Netherlands" (2007-2009)
Member of the Commission "Risks of dope in amateur sport" Health Council of The Netherlands of the Ministry of Health (2008- 2010)
Member of the Commission "Health and Environment" Health Council of The Netherlands of the Ministry of Health (2009-2015)

Scientific Committees:
Scientific Committee: Symposium Health Aspects Chemical Accidents; Emergency

Preparedness and Response. Utrecht 16-17 April 1993, The Netherlands
Scientific Committee: International Conference on the Health Aspects of Chemical Incidents. March 19-20, 1997, Birmingham, United Kingdom.
Scientific Committee: Scientific Meeting of the EAPCCT, July 2-5 1997, Oslo, Norway.
Scientific Committee: International Training Courses 1997; Advances in Clinical Toxicology: Environmental Toxicology and Common Drug Poisonings, November 19-21, 1997, Republic of San Marino.
Scientific Committee: XVIII International Congress of the EAPCCT March 24-28, 1998, Zurich, Switzerland.
Scientific Committee: Fourth World Conference on Injury Prevention and Control May 17-20, 1998, Amsterdam, The Netherlands.
Scientific Committee: XIX International Congress of the EAPCCT June 22-25, 1999, Dublin, Ireland.
Scientific Committee: XX International Congress of the EAPCCT May 2-5, 2000, Amsterdam, The Netherlands.
Chairman Scientific Committee: XXI International Congress of the EAPCCT May 16-19, 2001, Barcelona, Spain
Chairman Scientific Committee: XXII International Congress of the EAPCCT May 22-25, 2002, Lisbon, Portugal
Scientific Committee: XXIII International Congress of the EAPCCT May 20-23, 2003, Rome, Italy
Scientific Committee: XXIV International Congress of the EAPCCT June 1-4, 2004, Strasbourg, France
Scientific Committee: XXV International Congress of the EAPCCT May 10-13, 2005, Berlin, Germany
Abstract Review Committee: North American Congress of Clinical Toxicology, September 2005, Orlando, FL, USA
Scientific Committee: XXVI International Congress of the EAPCCT April 19-22, 2006, Prague, Czech Republic
Abstract Review Committee: North American Congress of Clinical Toxicology, 2006, San Francisco, CA, USA
Scientific Committee: XXVII International Congress of the EAPCCT May 1-4, 2007, Athens, Greece
Abstract Review Committee: North American Congress of Clinical Toxicology, 2007, New Orleans, LA, USA
Scientific Committee: XXVIII International Congress of the EAPCCT May 6-9, 2008, Seville, Spain
Abstract Review Committee: North American Congress of Clinical Toxicology, September 2008,Toronto, Ontario, Canada
Scientific Committee: XXIX International Congress of the EAPCCT May 12-15, 2009, Stockholm, Sweden
Abstract Review Committee: North American Congress of Clinical Toxicology, September 2009 San Antonio, USA
Scientific Committee: XXX International Congress of the EAPCCT May, 2010, Bordeaux, France
Abstract Review Committee: North American Congress of Clinical Toxicology October 2010, Denver, USA
Scientific and Meetings Committee of the European Association of Poisons Centres and Clinical Toxicologists (1996-2010)
Abstract Review Committee of the XXXI International Congress of the EAPCCT May, 2011, Dubrovnik, Croatia.
Abstract Review Committee: North American Congress of Clinical Toxicology October 2011, Washington, USA
Abstract Review Committee of the XXXII International Congress of the EAPCCT May-June, 2012, Londen, United Kingdom
Abstract Review Committee of the XXXIII International Congress of the EAPCCT 28-31 May 2013, Copenhagen, Denmark
Abstract Review Committee of the XXXIV International Congress of the EAPCCT 27-30 May 2014, Brussels, Belgium

Abstract Review Committee of the XXXV International Congress of the EAPCCT 26-29 May 2015, St. Julian's, Malta

Lecturer at the University Utrecht on Clinical Toxicology, Utrecht University, Utrecht, The Netherlands,
Faculty of Medicine 1986 - 2015
Faculty of Pharmacology 1989 - 2015
Faculty of Biology 1989 - 2015
Faculty of Veterinary Medicine 2007 - 2015

Editorial Board:
Nederlands Tijdschrift voor Intensive Care Geneeskunde (1999-2002)
Senior Editorial Board: Journal of Toxicology Clinical Toxicology (1997-2004)
Senior Editorial Board: Toxicological Reviews (2002-2004)
Deputy Editor: Clinical Toxicology (2004- 2015)

"Peer reviews" for:
Nederlands Tijdschrift voor Geneeskunde
The Netherlands Journal of Medicine
(Journal of Toxicology) Clinical Toxicology
Human and Experimental Toxicology
Intensive Care Medicine
Critical Care Medicine
European Journal of Internal Medicine
Nederlands Tijdschrift voor Intensive Care Geneeskunde
Journal of Neurology
Neuroscience Research Communications
British Medical Journal
Toxicology in Vitro

Scientific organizer of:
Module Clinical Toxicology, Utrecht, The Netherlands; 5 days annual course in the framework of the post-doctoral course for becoming Toxicologist in The Netherlands(1989 - 1996)
Post-doctoral course: Acute intoxications in the occupational setting. Bilthoven 27 March 1992.
Module Clinical and Forensic Toxicology, Utrecht, The Netherlands; 7 days annual course in the framework of the post-doctoral course for becoming Toxicologist in The Netherlands (1997 - 2013)
XXI International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), Barcelona, Spain 16-19 May, 2001
XXII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), Lisbon, Portugal 22-25 May, 2002

Scientific co-organization of:
Symposium Health Aspects Chemical Accidents; Emergency Preparedness and Response. Utrecht 16-17 April 1993
XX International Congress of the European Association of Poisons Centres and Clinical Toxicologists, Amsterdam, 2-5 May, 2000

Member of :
American Academy of Clinical Toxicology (AACT)
European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)
Dutch Society of Toxicology (NVT)
Royal Dutch Society of Medicine (KNMG)
Dutch Society of Internal Medicine (NIV)
Dutch Society of Intensive Care (NVIC)
Dutch Society of Clinical Pharmacy & Biopharmacy
Landelijke Vereniging van Artsen in Dienstverband (LAD)

Publications J. Meulenbelt
Peer reviewed

1. Brandjes DPM, Deventer SJH van, Meulenbelt J, Agenant DMA. Behandeling van een door embolie afgesloten arteria renalis met streptokinase in lage dosering. Ned Tijdschr Geneeskd 1985; 129: 1481-3.
2. Meulenbelt J, Wieling TW, Kager PA. Een acute ziekte met koorts, hoofdpijn, exantheem en verminderde nierfunctie: een spoedeisend geval. Ned Tijdschr Geneeskd 1986; 130: 1257-9.
3. Zwaveling JH, Kort WLAM de, Meulenbelt J, Hezemans-Boer M, van Vloten WA, Sangster B. Exposure of the skin to methyl bromide: A study of six cases occupationally exposed to high concentrations during fumigation. Hum Toxicol 1987; 6: 491-5.
4. Hezemans-Boer M, Toonstra J, Meulenbelt J, Zwaveling JH, Sangster B, Van Vloten WA. Skin Lesions due to Exposure to Methyl Bromide. Arch Dermatol 1988; 124: 917-21.
5. Meulenbelt J, Zwaveling JH, Zoonen P van, Notermans NC. Acute MCPP intoxication: Report of two cases. Hum Toxicol 1988; 7: 289-92.
6. Sangster B, Meulenbelt J. Acute Pulmonary intoxications. Overview and pratical guidelines (Review). Neth J Med 1988; 33: 91-100.
7. Zwaveling JH, Meulenbelt J, Xanten NHW van, Henee RJ. Renal failure associated with the use of dextran-40. Neth J Med 1989; 35: 321-6.
8. Haasnoot K, Vught AJ van, Meulenbelt J, Bergman LR. Acute blauwzuurvergiftiging bij een zuigeling. Ned Tijdschr Geneeskd 1989; 133: 1753-6.
8a. Ingezonden commentaar op artikel:"Acute blauwzuurvergiftiging bij een zuigeling". Ned Tijdschr Geneeskd 1989; 133: 2409.
8b. Ingezonden commentaar op artikel:"Acute blauwzuurvergiftiging bij een zuigeling". Ned Tijdschr Geneeskd 1990; 134: 182-3.
9. Meulenbelt J, Groot G de, Savelkoul TJF. Acute toluene intoxication, report of two cases. Br J Ind Med 1990; 47: 417-20.
10. Meulenbelt J, Sangster B. Acute nitrogen dioxide intoxication; clinic, pathophysiology and treatment (review). Neth J Med 1990; 37: 132-138.
11. Meulenbelt J, Dormans JAMA, Marra M, Rombout PJA, Sangster B. Rat model to investigate the treatment of acute nitrogen dioxide intoxication. Human and Exp Toxicol 1992; 11: 179-187.
12. Meulenbelt J, Bree L van, Dormans JAMA, Boink ABTJ, Sangster B. Biochemical and histological alterations in rats after acute nitrogen dioxide intoxication. Hum and Exp Toxicol 1992; 11: 189-200.
13. Hegger C, Savelkoul TJF, Meulenbelt J. Vergiftiging door lood. Ned Tijdschr Geneeskd 1992; 136: 1093-97.
14. Vloten WA van, Cooijmans ACM, Poel J, Meulenbelt J. Concentrations of nitrogen mustard in the air during topical treatment of patients with mycosis fungoides. Br J Dermatol 1993; 128: 404-406.
15. Hustinx WNM, Laar RTH van de, Huffelen AC van, Verwey JC, Meulenbelt J, Savelkoul TJF. Systemic effects following inhalational methylbromide poisoning: a study of 9 cases occupationallyexposed due to inadvertant spread during fumagation. Br J Ind Med 1993; 50: 155-159.
16. Meulenbelt J, Dormans JAMA, Bree L van, Rombout PJA, Sangster B. Desferrioxamine treatment reduces histological evidence of lung damage in rats after acute nitrogen dioxide (NO_2) intoxication. Hum and Exp Toxicol 1993; 12: 389-395.
17. Gelderen CEM van, Savelkoul TJF, Dokkum van W, Meulenbelt J. Motives and perception of healthy volunteers who participate in experiments. Eur J Clin Pharmacol 1993; 45: 15-21.
18. Hegger C, Steenis G van, Meulenbelt J. Rabies, en vaccinatie in Nederland. Ned Tijdschr Geneeskd 1993; 137: 1549-53.
19. Erich HE, Meulenbelt J. Behaarde rupsen, een oprukkend gevaar in Nederland. Ned Tijdschr Geneeskd 1993; 137: 1672-3.
20. Bartelink AKM, Kortbeek LM, Huidekoper HJ, Meulenbelt J, Knapen van F. Acute respiratory failure due to toxocara infection. Lancet 1993; 342: 1234.
21. Hustinx WNM, Meulenbelt J. Verkoudheid, acute sinusitis en acute tonsillitis.In: Volksgezondheid Toekomst Verkenning. Den Haag: Sdu Uitgeverij Plantijnstraat 1993: 402-5.

22. Hustinx WNM, Meulenbelt J. Longontsteking en acute bronc(iol)itis. In: Volksgezondheid Toekomst Verkenning. Den Haag: Sdu Uitgeverij Plantijnstraat 1993: 406-10.
23. Meulenbelt J. Experimental study to investigate the effects of intervention in acute nitrogen dioxide intoxication to improve human treatment. Thesis University Utrecht 1994.
24. Boink ABTJ, Wemer J, Meulenbelt J, Vaessen HAMG, Wildt DJ de. The mechanism of fluoride induced hypocalcemia. Hum and Exp Toxicol 1994; 13: 149-155.
25. Toet AE, Dijk A van, Savelkoul TJF, Meulenbelt J. A case of severe mercury chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS).Hum and Exp Toxicol 1994; 13: 11-16.
26. Meulenbelt J, Bree L van, Dormans JAMA, Sangster B. No beneficial effect of N-acetylcysteine treatment on broncho-alveolar lavage fluid variables in acute nitrogen dioxide intoxicated rats. Hum and Exp Toxicol 1994; 13: 472-477.
27. Meulenbelt J, Bree L van, Dormans JAMA, Boink ABTJ, Sangster B. Development of a rabbit model to investigate the effects of acute nitrogen dioxide intoxication. Human and Experimental Toxicology 1994; 13: 749-758.
28. Gelderen CEM van, Olling M, Barends D, Meulenbelt J, Rauws AG, Salomons P. Biovailability of diclofenac administered as different enteric coated tablets to healthy volunteers with normal and artificially increased pH of the stomach. Biopharmaceutics & Drug Disposition 1994; 15: 775-788.
29. Kortbeek LM, Veldkamp KE, Bartelink AKM, Meulenbelt J, Knapen F van. Ernstige pneumonie ten gevolge van infectie met Toxocara. Ned Tijdschr Geneeskd 1994; 2581-84.
30. Jansen EHJM, Berg RH van den, Boink ABTJ, Hegger C, Meulenbelt J. A new physiological biomarker for nitrate exposure in humans. Toxicol Lett 1995; 77: 265-9.
31. Boink ABTJ, Meulenbelt J, Wemer J, Vaessen HAMG, Dortant P, Wildt DJ de. Systemic fluoride poisoning following dermal hydrofluoric acid exposure: development of an intravenous sodium fluoride infusion model in rats. J Toxicol Cut Ocular Toxicol 1995; 14 (2): 75-87.
32. Zoelen GA van, Vries I de, Meulenbelt J. Verontrustende toename van intoxicaties door deptropine. Ned Tijdschr Geneeskd 1996; 98-99.
33. Toet AE, Biesebeek JD te, Vleeming W, Wemer J, Meulenbelt J, Wildt DJ de. Reduced survival after isoprenaline/dopamine in d,l-propranolol intoxicated rats. Human Exp Toxicol 1996; 15: 120-8.
34. Emergency procedures in the event of chemical exposure/accidents. Meulenbelt J. Medical Review (Przeglad Lekarski) 1996; 53: 220-24.
35. Toet AE, Wemer J, Vleeming W, Biesebeek JD te, Meulenbelt J, Wildt DJ de. Experimental study of the detrimental effect of dopamine/glucagon combination in d,l-propranolol intoxication. Human Exp Toxicol 1996; 15: 411-21.
36. Peeters CCAM, Rümke HC, Sundermann LC, Rouppe van der Voort EM, Meulenbelt J, Schuller M, Kuipers AJ, Ley P van der, Poolman JT. Phase I clinical trial with a hexavalent PorA containing meningococcal outer membrane vesicle vaccine. Vaccine 1996; 14: 1009-15
37. Beltman W, Vries I de, Meulenbelt J. Praktische richtlijnen voor diagnostiek en behandeling van paddestoelvergiftigingen. Ned Tijdschr Geneeskd 1996; 140: 1894-99.
38. Markhorst DG, Leenhoven T, Uiterwijk JW, Meulenbelt J, Vugt AJ van. Occupational exposure by nitric oxide inhalational therapy in a pediatric intensive care setting. Intensive Care Medicine 1996; 22: 954-58.
39. Toet AE, Kuil A van de, Vleeming W, Wemer J, Bode W, Meulenbelt J, Wildt DJ de. Toxic doses of rac-,(-)-(s)- and (+)-(R)-propranolol in rats and rabbits. Chirality 1996: 8; 411-17.
40. Meulenbelt J, Vries I de. Acute work-related poisoning by pesticides in The Netherlands; a one year follow-up study. Medical Review (Przeglad Lekarski) 1997; 54 (10) 665-70
41. Otterdijk F van, Vries I de, Meulenbelt J. Een pijnlijke ontmoeting met de pieterman (Echiichtis vipera). Ned Tijdschr Geneeskd 1997; 141: 1428-30
42. Vleeming W, Kuil A van de, Biesebeek JD te, Meulenbelt J, Boink ABTJ. Effect of nitrite on blood pressure in anaesthetized and free-moving rats. Food Chem Toxicol 1997; 35: 615-19
43. Wemer J, Tamminga W, Oosterhuis B, Wilffert B, Jonkman J, Ley L de, Zeeuw R de, Herings R, Vranckx S, Drenth B, Meulenbelt J. Genotyping in relation to pharmacokinetics and pharmacodynamics. Conceptuur 1997; 14: 34-6

44. Meulenbelt J, Joore JCA. Incidents cliniques suite à la consommation supposée d'Ecstasy ou de drogues apparentées. Les Cahiers de Prospective Jeunesse 1998; 3 (2) 25-26
45. Boereboom FTJ, Dijk A van, Zoonen P van, Meulenbelt J. Nonaccidental endosulfan intoxication: A case report with toxicokinetic calculations and tissue concentrations. J Toxicol Clin Toxicol 1998; 36: 345-352
46. Mensinga TjT, Meulenbelt J. Human volunteer studies in consumer product research. Neth J Med 1998; 52: 129-130
47. Vries I de, Spaans E, Dijk A van, Meulenbelt J. Lead toxicokinetics. Development of a biokinetic model to understand and predict the outcome of treatment. Medical Review (Przeglad Lekarski) 1998; 55: 500-504
48a Zoelen GA van, Vries I de, Meulenbelt J. Risico's van ingestie van reinigingstabletten voor kunstgebitten en gebitsprothesen. Ned Tijdschr Geneeskd 1998; 142: 2408-11
48b Zoelen GA van, Vries I de, Meulenbelt J. Risico's van ingestie van reinigingstabletten voor gebitsprothesen Ned Tijdschr Tandheelkd 1999; 106: 94-96
49. Meulenbelt J, Mensinga TjT, Kortboyer JM, Speijers GJA, Vries I de. Healthy volunteer studies in Toxicology. Toxicol Lett 1998; 102-103: 35-39
50. Olling M, Mensinga TjT, Barends DM, Groen C, Lake OA, Meulenbelt J. Bioavailability of carbamazepine from four different products and the occurrence of side effects. Biopharm Drug Dispos 1999; 20: 19-28
51. Meulenbelt J. Ammonia. Medicine 1999; 27: 21
52. Meulenbelt J. Chlorine. Medicine 1999; 27: 31-32
53. Meulenbelt J. Nitrogen and nitrogen oxides. Medicine 1999; 27: 49
54. Ploeger BA, Meulenbelt J, DeJongh J. Physiology based pharmacokinetic modeling of glycyrrhizic acid, a compound subject to presystemic metabolism and enterohepatic cycling. Toxicol Appl Pharmacol 2000; 162: 177-188
55. Boereboom FTJ, Ververs FFT, Meulenbelt J, Dijk A van Hemoperfusion is ineffectual in severe chloroquine poisoning. Crit Care Med 2000; 28: 3346-3350
56. Ververs FFT, Dijk A van, Vinks SATMM, Blankestijn PJ, Savelkoul TJF, Meulenbelt J, Boereboom FTJ. Pharmacokinetics and dosing regimen of meropenem in critically ill patientsreceiving continuous venovenous hemofiltration. Crit Care Med 2000; 28: 3412-3416
57. Ploeger B, Mensinga TjT, Sips A, Meulenbelt J, DeJongh J. A human physiologically-based pharmacokinetic/pharmacodynamic model for glycyrrhizic acid, a compound subject to presystemic metabolism and enterohepatic cycling. Pharm Res 2000; 17: 1516-1525
58. Ploeger B, Mensinga TjT, Sips A, Deerenberg C, Meulenbelt J, DeJongh J. A population physiologically based pharmacokinetic/pharmacodynamic model for the inhibition of 11-β-hydroxysteroid dehydrogenase activity by glycyrrhetic acid. Toxicol Appl Pharmacol 2001; 170: 46-55
59. Ploeger B, Mensinga TjT, Sips A, Seinen W, Meulenbelt J, DeJongh J. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. Drug Metab Rev 2001; 33: 125-147
60. Tobé TJM, Braam BG, Meulenbelt J, Dijk GW van. Ethylene glycol poisoning mimicking snow white. Lancet 2002; 359: 444-445
61. Riel AJHP van, Vries I de, Meulenbelt J. Wat er gebeurt als u het Nationaal Vergiftigingen Informatie Centrum belt. Tijdschrift voor Huisartgeneeskunde 2002; 19: 210 -215
62. Leenders MEC, Tobé TJM, Vries I de, Meulenbelt J. Acute rabdomyolyse bij patiënten met intoxicaties. Een aandoening om in het achterhoofd te houden. Pharm Weekbl 2003; 138: 26-31
63. Riel AJHP van, Vries I de, Meulenbelt J. Intoxicaties: kerngetallen en trends. Achter de schermen van het NVIC. Pharm Weekbl 2003; 138: 4-9
64. Touw DJ, Grouls R, Vries I de, Meulenbelt J, Uges DRA. Absorptieverminderende technieken in de toxicologie. Dubbelblind vergelijkend onderzoek is niet beschikbaar. Pharm Weekbl 2003; 138: 16-19
65. Ververs FFT, Tobé TJM, Meulenbelt J. Hemodialyse en andere technieken. Richtlijnen voor de praktijk. Pharm Weekbl 2003; 138: 20-25
66. Mensinga TjT, Speijers GJA, Meulenbelt J. Health Implications of Exposure to Environmental Nitrogenous Compounds. Toxicol Rev 2003; 22: 41-51
67. Joore JCA, Leeuwen HJ van, Meulenbelt J, Tobé TJM, Fijen JW. Pro/Con Debate of Activated Protein C in Severe Sepsis. Crit Care Med 2003; 31: 2249

68. Van Riel AJHP, de Vries I, Meulenbelt J. Gezondheidsrisico's door Ephedra in voedingssupplementen. Ned Tijdschr Geneeskd 2003; 147: 2017-2019
69. Riel AJHP van, Vries I de, Meulenbelt J. Aantal vragen over rabiësblootstelling blijft gelijk. Infectieziekten Bulletin 2003; 14: 414
70. Meulenbelt J. Ammonia. Medicine, 2003; 31:30-31
71. Meulenbelt J. Chlorine. Medicine 2003; 31: 42
72. Meulenbelt J. Nitrogen and Nitrogen Oxides. Medicine 2003; 31: 64
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248. Roelen CCJ, van Riel AJHP, Mulder-Spijkerboer HN, de Vries I, Meulenbelt J. Improving the use of the Dutch Poisons Information Website and the effect on telephone call volume. - 2015. 14th APAMT International Scientific Conference in Perth, Western Australia - 1-4 December 2015. (Poster)
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252. van Velzen AG, van Sommeren-de Potter IC, den Dulk MO, van Riel AJHP, Meulenbelt J, de Vries I. Attempted suicide by ingestion of ricin soup. XXXV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 26-29 May 2015, St Julian's, Malta. Clin Toxicol 2015;53(4):346. (Poster)
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260. Roelen CCJ, van Riel AJHP, Venhuis BJ, de Vries I, Meulenbelt J. A weight loss product containing fluoxetine. 36th International Congress of the European Association of Poisons

Centres and Clinical Toxicologists (EAPCCT) 24-27 May, 2016, Madrid, SpainClin Toxicol 2016;54(4):468-9. (Poster)
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16.1.7 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.

Sponsor or legal representative:
Prof. W.A. van Klei, MD, PhD, Research Manager,
Division of Anesthesiology, Intensive Care and Emergency Medicine, University Medical Center Utrecht

30-11-16

Principal investigator:
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National Poisons Information Center and Intensive Care
Division of Anesthesiology, Intensive Care and Emergency Medicine
University Medical Center Utrecht

28-11-2016

16.1.8 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
Not applicable

16.1.9 Randomization scheme and codes (patient identification and treatment assigned)
No randomization was performed

16.1.10 Audit certificates (if available)
All certificates can be obtained from the investigators of the study if needed

16.1.11 Documentation of statistical methods
Not applicable

16.1.12 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

All laboratories were CCKL and GCP accredited: Clinical Pharmacy of the University Medical Center Utrecht (UMCU), Clinical Chemistry Laboratory of the UMCU and University Medical Center of Leiden (LUMC), and the Clinical Genetic Laboratory of the Erasmus Medical Center Rotterdam. Documentation can be derived at the investigators.

16.1.13 Publications based on the study
Not available

16.1.14 Important publications referenced in the report
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16.2.1 Patient Data Listings
Not available

16.2.2 Discontinued patients
All patients have completed the study

16.2.3 Protocol deviations
No protocol deviations have been made

16.2.4 Patients excluded from the efficacy analysis
This is no efficacy study

16.2.5 Demographic data
Listed in paragraph 14.2 table 1.

Missing data	
UTN 6	No urine collection at month 3 and 6
UTN 9	No urine collection at month 3
UTN 19	No urine collection at month 3
UTN 21	No urine collection at month 3

16.2.6 Compliance and/or Drug Concentration Data (if available)
Not available

16.2.7 Individual Efficacy Response data
Not applicable

16.2.8 Adverse event listings per patient

	Recording 12-06-2013 to 14-12-2013	
Patient trial number Number	AE brief discription	Date
UTN.SPART.001	1. Mech. ventilation (>1 day) 2. Resurgery because of blood clot 3. Readmission cellulitis necrosis of digital 1 4. Readmission Temp high, CMV infection 5. Readmission Active CMV infection, recurrent giant cell myocarditis 6. 12/6 - 10/7 severe anemia Hb<7 7. 19/6 - 27/6 hypomagnesemia: mg<0,6 8. 12/6 - 26/6 hypoalbuminmia: albumin <30	12-6-2013 12-6-2013 3-7-2013 25-7-2013 14-8-2013 10-7-2013 27-6-2013 26-6-2013
UTN.SPART.002	10/7 - 11/7 severe anemie Hb<7	11-7-2013
UTN.SPART.003	1. Reoperation because of pleural blood clot 2. Renal dysfunction: combination shock, inflammation and drugs 3. Suspected rejection, primary graft dysfunction 4. Hypernatremia 5. 9/7 - 29/7 Severe anemia Hb<7 6. 9/7 - 25/7 Disturbances of proteins albumin<30 7. Readmission: bacterial Infection 8. Readmission: bacterial infection, sputum plugging	9-7-2013 12-7-2013 13-7-2013 14-7-2013 29-7-2013 25-7-2013 14-10-2013 22-11-2013
UTN.SPART.004	Severe anemia Hb<7	20-8-2013
UTN.SPART.005	1. 13/9 - 4/10 Severe anemia Hb<7 2. Prolonged mechanical ventilation (>1 day) 3. 14/9 - 27/9 Hypoalbuminmia: albumin <30	4-10-2013 18-9-2013 27-9-2013
UTN.SPART.006	1. Repeated surgery on 5/10; 6/10;13/10 and 14/10 2. 5/10 - 28/11 Severe anemia 3. 6/10 - 21/11 Severe electrolyte disturbance Mg <0.6 4. 10/10 - 22/10 Disturbances of proteins Albumin<30 5. 23/10 - 25/10 Decubitus 6. 5/10 - 7/11 Prolonged mechanical ventilation (.1 day) 7. 5/10 and 6/10 Wound complications, serious bleeding (>1000ml)	14-10-2013 28-11-2013 21-11-2013 22-10-2013 25-10-2013 7-11-2013 6-10-2013
UTN.SPART.007	1. 13/11 - 18/11 Prolonged mechanical ventilation (.1 day) 2. 13/11 -2/12 Severe Anemia Hb<7 3. 14/11 – 19/11 Disturbances of proteins 4. Severe electrolyte disturbance Mg<0.6 5. 13/11 – 4/12 Renal dysfunction	18-11-2013 2-12-2013 19-11-2013 13-11-2013 4-12-2013
UTN.SPART.008	1. 16/11 – 14/12 Severe anemia Hb>7 2. 16/11 -22/11 Severe electrolyte disturbances: Mg<0.6 3. 16/11 – 17/11 Severe electrolyte disturbances: Phosphate <0.6 4. 16/11 – 14/12 Disturbances of proteins Albumin<30	14-12-2013 22-11-2013 17-11-2013 14-12-2013
UTN.SPART.009	1. 23/11 – 14/12 Severe Anemia Hb<7 2. 23/11 – 14/12 Disturbances of proteins Albumin<30 3. Severe electrolyte disturbances Mg<0.6 at 13/11; 3/12; 6/12	14-12-2013 14-12-2013 6-12-2013
UTN.SPART.010	1. Repeated surgery 2. 27/11 – 29/11 Serious bleeding >1000 ml/day 3. 27/11 – 01/12 Prolonged mechanical ventilation >1 day 4. 27/11 – 14/12 Severe anemia Hb<7 5. 27/11 – 14/12 Disturbances of proteins albumin<30 6. 29/11 – 2/12 Decubitus 7. Sever electrolyte disturbances phosphate<0.6	28-11-2013 29-11-2013 01-12-2013 14-12-2013 14-12-2013 2-12-2013 27-11-2013
UTN.SPART.011	1. 3/12 – 5/12 Prolonged mechanical ventilation (>1day) 2. 3/12 – 14/12 Severe anemia Hb<7 3. 3/12 – 14/12 Disturbances of proteins Albumin<30 4. Delirium (start Haldol)	5-12-2013 14-12-2013 14-12-2013 6-12-2013

	Recording 12-06-2013 to 14-12-2013	
UTN.SPART.012	1. Repeated surgery, suspected tamponed 2. 4/12 – 13/12 Prolonged mechanical ventilation (.1 day) 3. 4/12 – 14/12 Severe Anemia Hb<7 4. 4/12 - 14/12 Disturbances of proteins	4-12-2013 13-12-2013 14-12-2013 14-12-2013

	Recording 06-12-2013 to 21-07-2014	
Patient trial Number	(S)AE brief description	Date
UTN.SPART.005	1. 6/12 ECV because of atrial flutter: Arrhythmias	6-12 -2013
UTN.SPART.007	1. 19/12 Severe anemia: Hb<7	19-12-2013
UTN.SPART008	1. 14/12 -16/12 Severe anemia: Hb< 2. 14/12 -16/12 Disturbances of protein	16-12-2013 16-12-2013
UTN.SPART.009	1. 14/12- 26/6 Severe anemia: Hb<7 2. 13/3;23/5;24/6;2/7;9/7 Readmission Temp high	14-12-2013
UTN.SPART.010	1. 27/11 Severe anemia: Hb<7 2. 14/12 Disturbances of protein: hypoalbuminmia <30	14-12-2013
UTN.SPART.011	1. 14/12 – 23/12 Severe anemia: Hb<7	23-12-2013
UTN.SPART.012	1. 10/12 Repeated surgery, ECMO removal 2. 02/01 Implant pacemaker 3. 14/12 – 14/01 Severe anemia: Hb <7 4. 14/12 – 20/12 Disturbances of proteins: hypoalbuminmia; albumin <30 5. 14/12- 23/12 Decubitus (left heel)	23-12-2013
UTN.SPART.013	1. 23/12 – 7/7 Severe anemia: Hb<7 2. 23/12 severe electrolyte disturbances: hypophosphatemia phosphate <0.6 3. 23/12 – 2/1 Disturbances of proteins: hypoalbuminmia: albumin <30 4. 3/4-28/4 readmission: pancytopenia due to drugs other than tacrolimus + SCID in medical history and suspected TPMT/y	23-12-2013
UTN.SPART.014	1. 24/12 – 7/1 Severe anemia: Hb<7 2. 24/12 severe electrolyte disturbances: hypomagnesemia 3. 24/12 – 29/12 Disturbances of proteins: hypoalbuminmia 4. 24/12 – 7/1 Prolonged mechanical ventilation (>1day) 5. 31/12 Repeated surgery, ECMO remove 6. 3/1- Decubitus(groin)	7-1-2014
UTN.SPART.015	1. 26/12 – 19/2 Severe anemia: Hb<7 2. 25/12 – 2/1 hypoalbuminmia <30 g/L	19-2-2014

	Recording 06-12-2013 to 21-07-2014	
UTN.SPART.016	1. 8/1 – 7/7 Severe anemia: Hb<7 2. 8/1 – 20/1 Disturbances of proteins: albuminmia <30 g/L 3. 8/1 sever electrolyte disturbances: hypophosphatemia <0.6 mmol/L; hyperkalemia>5.5 4. 3/3 – 7/3 readmission decreased lung function 5. 30/6 ferro infusion	30-6-2014
UTN.SPART.017	1. 5/3 – 8/4; 22/4 – 3/7 Severe anemia: Hb<7 2. 5/3 – 7/3 disturbances of proteins: albuminmia<30 g/l 3. Severe electrolyte disturbances: 6/3 hypermagnesemia: >1.2 mmol/L; 14/3 hypomagnesemia<0,6 mmol/L	14-03-2014
UTN.SPART.018	1. 6/3 Severe anemia: Hb<7 2. 7/3 disturbances of proteins: hypoalbuminmia<30 g/L 3. 6/3 Severe electrolyte disturbances: hypomagnesemia<0,6 mmol/L	7-3-2014
UTN.SPART.019	1. 18/3 – 21/5 Severe anemia: Hb<7 2. 18/3 – 27/3 Disturbances of proteins: hypoalbuminmia<30 g/L 3. 17/7 readmission, decreased lung function, high temp: infection	17-07-2014
UTN.SPART.020	1. 12/4 – 5/5 Severe anemia: Hb<7 2. 12/4 -28/4 disturbances of proteins: Hypoalbuminmia<30 g/L 3. 30/4 – 26/5 severe electrolyte disturbances: hypophosphatemia<0.6 mmol/L	26-05-2014
UTN.SPART.021	1. 26/4 – 18/5 prolonged mechanical ventilation>1 day 2. 27/4 – 18/5 Severe anemia: Hb<7 3. 26/4 – 15/5 disturbances of proteins: hypoalbuminmia<30 g/L 4. 18/5-27/5; 30/5-6/6 severe electrolyte disturbances hypomagnesemia<30 mmol/L 5. 29/4 Ok, ECMO remove 6. 5/5 invasive aspergillosis (infection); pulmonary emboli; paroxysmal atrial fibrillation (arrhythmias) 7. 1/7 – 11/7 Decreased lung function, suspected rejection	11-07-2014
UTN.SPART.022	1. 18/5 – 20-5; 22/5- 25/5 prolonged mechanical ventilation (>1day) 2. Severe anemia: Hb<7 3. 22/5-25/5 delirium 4. 18/5 – 6/6/ disturbances of proteins: hypoalbuminmia<30 g/L	6-6-2014

	Recording 06-12-2013 to 21-07-2014	
	5. 23/5 ; 6/6 severe electrolyte disturbances hypomagnesemia <0.6 mmol/L hypernatremia>130mmol/L	
UTN.SPART.023	1. 24/5 – 21/7 Severe anemia: Hb<7 2. 24/5 – 23/6 Disturbances of proteins: hypoalbuminmia<30 g/L 3. 13/6 – 14/6 severe electrolyte disturbances: hypomagnesemia<0.6 mmol/L	21-7-2014

☐ Continued on next page. (Add pages as required. Please complete header section on all pages.)

SAE recording	**Log 15-07-2014 tm 15-01-2015**	**IMP**
Study subject ID/age/gender (m/w)	(S)AE nr/date of onset and end of event/SAE brief description/outcome/expected yes(y) or (n)	Name/dose (AP=as prescribed)/route/starting date, tacrolimus after transplantation as lifelong daily treatment/causality y or n
UTN.SPART.018	3. SAE/31/7 -2/8 readmission: shunt placement 4. SAE/14/8-20/8 readmission: bronchoscopy 5. SAE/15/7-18/7 readmission: infection 6. SAE/31/7 severe anemia: Hb<7/resolved/y	Tacrolimus/AP/orally/06-03-2014/n Tacrolimus/AP/orally/06-03-2014/n Tacrolimus/AP/orally/06-03-2014/n Tacrolimus/AP/orally/06-03-2014/n
UTN.SPART.020	2. SAE/7/8-9/8: readmission: balloon dilatation 3. SAE/28/11-2/12: readmission lung abscess	Tacrolimus/AP/orally/12-04-2014/n Tacrolimus/AP/orally/12-04-2014/n
UTN.SPART.021	6. SAE/29/7-30/7 readmission: to remove sternum wire. 7. SAE/15/12-16/12 readmission: infection	Tacrolimus/AP/orally/25-04-2014/n Tacrolimus/AP/orally/25-04-2014/n
UTN.SPART.023	7. SAE/5/8-7/8: readmission: infection	Tacrolimus/AP/orally/24-05-2014/n
UTN.SPART.024	3. SAE/22/9-15/10: severe anemia: Hb<7	Tacrolimus/AP/orally/22-09-2014/n
UTN.SPART.025	1. SAE/25/9-8/10: severe anemia: Hb<7 2. SAE/26/9: severe electrolyte disturbances: Hypophosphatemia<0.6 mmol/l 3. SAE/26/9-8/10: disturbances of proteins: hypoalbuminmia<30 g/l 4. SAE/2/10-5/10: encephalopathy or delirium: delirium	Tacrolimus/AP/orally/25-09-2014/n Tacrolimus/AP/orally/25-09-2014/n Tacrolimus/AP/orally/25-09-2014/n Tacrolimus/AP/orally/25-09-2014/n
UTN.SPART.026	4. SAE/21/10-6/11: severe anemia: Hb<7 5. SAE/28/10: severe electrolyte disturbances: Hypomagnesemia<0.6 mmol/l 6. SAE/21/10-6/11: disturbances of proteins: hypoalbuminmia<30 g/l	Tacrolimus/AP/orally/21-10-2014/n Tacrolimus/AP/orally/21-10-2014/n Tacrolimus/AP/orally/21-10-2014/n

SAE recording	Log 15-07-2014 tm 15-01-2015	IMP
UTN.SPART.028	4. SAE/18/11-12/01: severe anemia: Hb<7 5. SAE/18/11-31/12 disturbances of proteins: severe hypoalbuminmia < 30 g/l 6. SAE/19/11+23/11+26/11: severe electrolyte disturbances: severe hypermagnesemia >1.2 mmol/l 7. SAE/18/11-2/12: prolonged mechanical ventilation (>1 day) 8. SAE/19/11: repeated surgery; remove ECMO	Tacrolimus/AP/orally/18-11-2014/n Tacrolimus/AP/orally/18-11-2014/n Tacrolimus/AP/orally/18-11-2014/n Tacrolimus/AP/orally/18-11-2014/n Tacrolimus/AP/orally/18-11-2014/n

Subject ID	Date of report	Topic Summary	Reference			
		e.g. 'Patient xxx hospitalized because of xxx', etc. ***Name/dose (AP=as prescribed)/route/starting date, tacrolimus after transplantation as lifelong daily treatment/causality y or n**	SAE/SAR/SUSAR/SADE			
UTN.SPART.028	01/04/2015-02/04/2015	Readmission: Bronchoscopy with laser treatment both sides due to stenosis ***Tacrolimus/AP/orally/18-11-2014/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
UTN.SPART.029	28/01/2015-11/02/2015	Severe anemia: Hb< 7 mmol/L ***Tacrolimus/AP/orally/18-11-2014/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	13/07/2015	Severe hyponatremia: Na<130 mmo/L ***Tacrolimus/AP/orally/18-11-2014/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
			SAE SUSAR	X ☐	SAR SADE	☐ ☐
			SAE SUSAR	X ☐	SAR SADE	☐ ☐
			SAE SUSAR	X ☐	SAR SADE	☐ ☐
			SAE SUSAR	X ☐	SAR SADE	☐ ☐
	01/07/2015-08/07/2015	Readmission: DIOS(distal Intestinal Obstruction Syndrome) ***Tacrolimus/AP/orally/18-11-2014/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
UTN.SPART.030	24/02/2015-08/03/2015 11/03/2015-13/03/2015 18/03/2015-25/03-2015 09/05/2015-03/06/2015 05/07/2015-05/08/2015	Severe anemia: Hb< 7 mmol/L ***Tacrolimus/AP/orally/18-11-2014/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	24/2; 11/5; 29/05/2015-08/06/2015	Severe electrolyte disturbances: hypomagnesemia<0.6 mmol/L ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	24/02/2015	Severe electrolyte disturbances: hypermagnesemia>1.2 mmol/L ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	18/05/2015	Severe electrolyte disturbances: hyperkalemia>5.5 mmol/L ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	24/02/2015-13/03/2015 18/03/2015-23/03/2015 04/05/2015-01/06/2015 06/07/2015-16/07/2015 23/07/2015	Disturbances of proteins: hypoalbuminmia <30 g/l ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐

Subject ID	Date of report	Topic Summary	Reference			
	7/4/2015-14/04/2015	Readmission/ Bowel disturbances: Obstipation ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	26/4/2015-09/06/2015	Readmission: Pulmonary Infection ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	11/06/2015-15/06/2015	Readmission: DIOS (Distal Intestinal Obstruction Syndrome) ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	29/06/2015-31/07/2015	Readmission: Pulmonary Abscess ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐
	05/08/2015	Readmission: Insert Intravenous infusion ***Tacrolimus/AP/orally/24-02-2015/n**	SAE SUSAR	X ☐	SAR SADE	☐ ☐

16.2.9. Listing of individual laboratory measurements by patient, when required by regulatory authorities

Individual laboratory measurements by patients are not required by regulator authorities.

16.3 Case Report Forms

16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

No deaths or withdrawals have occurred.

16.3.2 Other CRFs submitted

Not applicable

6.4. Individual Patient Data Listings (US Archival Listing)

Not available

ANNEX I

Name of Sponsor/Company: University Medical Center Utrecht	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use only)*
Name of Finished Product: Not applicable	Page:	
Name of Active Ingredient: tacrolimus		

Criteria for evaluation:
Efficacy Not applicable

Safety Not available

Statistical methods:Not available

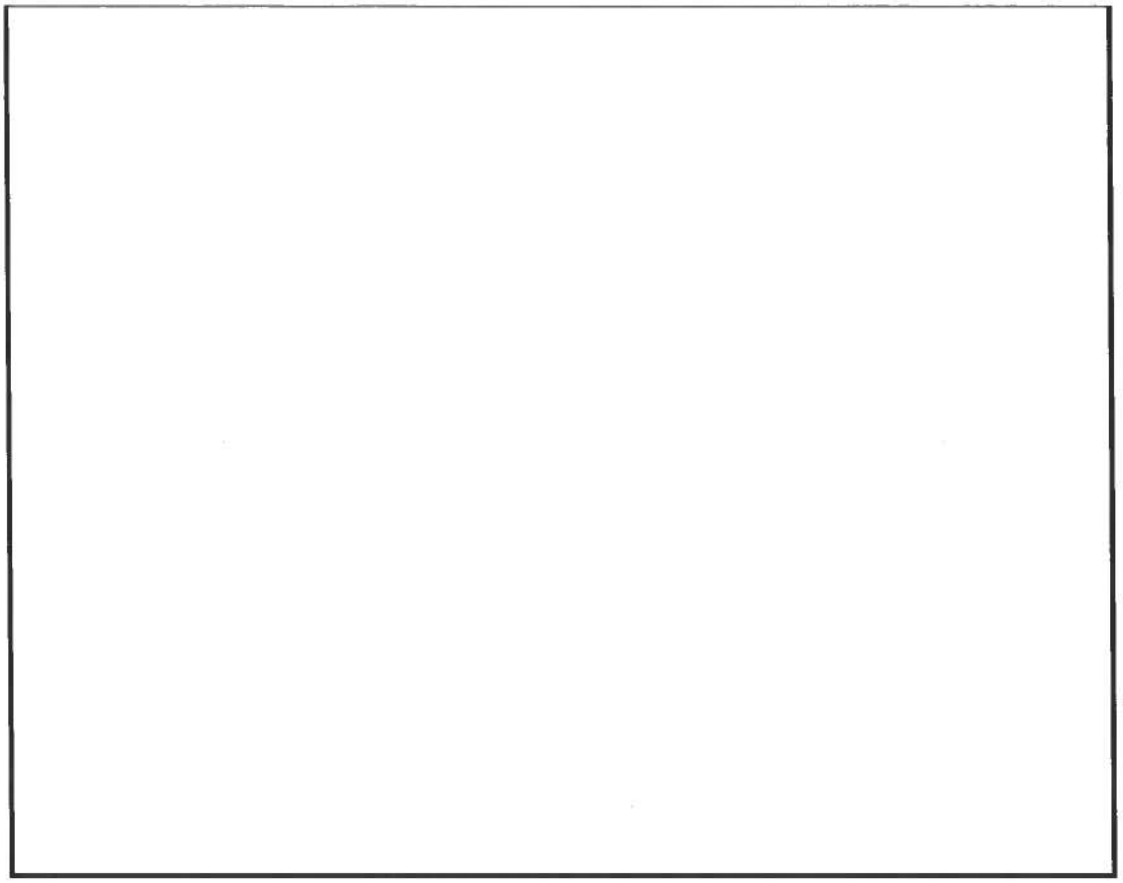
Summary – Conclusions Not available

Efficacy Results:Not applicable

Safety Results: Not available

Conclusion Not available

Date of report 24-11-2016



ANNEX II

SPONSOR'S RESPONSIBLE MEDICALOFFICER
SIGNATURE

_____

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

STUDY AUTHOR(S): Sikma M.A., MD
Lange D.W., MD PhD
Hunault C.C., MD PhD

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

SPONSOR'S RESPONSIBLE
MEDICAL OFFICER
AFFILIATION:

Prof. W.A. van Klei, MD, PhD, Research Manager,
Division of Anesthesiology, Intensive Care and Emergency Medicine, University Medical Center Utrecht

_____

DATE: 30-11-16

ANNEX III

GUIDANCE FOR SECTION 11.4.2 - STATISTICAL/ANALYTICAL ISSUES AND APPENDIX 16.1.9

A. STATISTICAL CONSIDERATIONS

Not available.

B. FORMAT AND SPECIFICATIONS FOR SUBMISSION OF DATA REQUESTED BY REGULATORY AUTHORITY'S STATISTICAL REVIEWERS

Not available.