SYNOPSIS CLINICAL STUDY REPORT

according to ICH E3 guideline

version 1.0 F, 21.01.2025

SIX MONTH, MULTI-CENTER, OPEN-LABEL, PROSPECTIVE, RANDOMIZED TRIAL, INVESTIGATING A STANDARD REGIMEN OF AN ADVAGRAF BASED IMMUNOSUPPRESSIVE REGIMEN IN DE-NOVO RENAL TRANSPLANT PATIENTS VERSUS A SLOWER DOSE TAPERING AND LOWER STARTING DOSE OF ADVAGRAF

S&L

Trial Protocol version 2.0F, 23.07.2014 amended by

amendment 01 version 1.0F, 29.05.2017;

Protocol V3.0F, 20.12.2017 and Protocol V3.1F, 20.03.2018

Sponsor	**Technische Universität Dresden** 01062 Dresden
Principal Coordinating Investigator	**Prof. Dr. Christian Hugo** Medizinische Fakultät Carl Gustav Carus der TU Dresden Medizinische Klinik und Poliklinik III Abteilung für Nephrologie/Dialyse Fetscherstraße 74, 01307 Dresden
Sponsor Code:	TUD-SplusL-061
EudraCT-Number:	2013-001770-19
Name of Finished Product and Active Substance	Finished Product: Advagraf® Active Substance: Tacrolimus

TABLE OF CONTENTS

TABLES AND FIGURES

1 SUMMARY OF TRIAL INFORMATION

Sponsor	**Technische Universität Dresden** 01062 Dresden
Principal Coordinating Investigator	Prof. Dr. Christian Hugo Medizinische Fakultät Carl Gustav Carus der TU Dresden Medizinische Klinik und Poliklinik III Abteilung für Nephrologie/Dialyse Fetscherstr. 74 01307 Dresden
Full Title	Six month, multi-center, open-label, prospective, randomized trial, investigating a standard regimen of an Advagraf based immunosuppressive regimen in de-novo renal transplant patients versus a slower dose tapering and lower starting dose of Advagraf
Short Title	S&L
Trial Protocol	Trial Protocol version 2.0F, 23.07.2014 amended by amendment 01 version 1.0F, 29.05.2017; Protocol version 3.0F, 20.12.2017 and Protocol version 3.1F, 20.03.2018
Indication	adult allograft recipients with normal immunological risk profile scheduled for primary or secondary kidney transplantation
Phase of development	IV
Study design	two armed, randomized, controlled, open-labelled, multicenter, non-inferiority
Objective(s) of the clinical trial	<u>Primary objective(s):</u> To demonstrate non-inferiority of biopsy-proven rejection and/or graft loss and/or patient death in the study group with slower dose tapering and lower starting dose of Advagraf compared with an standard Advagraf based immunosuppressive regimen. <u>Secondary objectives:</u> To assess • rate of necessary dose modifications in order to achieve tacrolimus target levels in the early postoperative period • renal function defined by need for renal replacement therapy as well as by means of glomerular filtration rate • rate of delayed graft function (DGF) • Incidence of bacterial or viral infections, in particular polyomavirus infection • Incidence of new onset diabetes mellitus after transplantation (NODAT) • Incidence of: o malignant tumors o fractures o heart failures o myocardial infarction

	o venous thrombosis o peripheral- and cerebrovascular diseases o hyperlipoproteinemia o arterial hypertension o anemia o cardiovascular mortality • rate of chronic-humoral rejections • changes in histology • rate of donor specific antibodies
Endpoints of the clinical trial	Primary Endpoint: occurrence of biopsy-proven rejection (according to Banff classification), or graft loss, or patient death within 6 months after transplantation Secondary Endpoints: Efficacy • creatinine 5 days, 4 weeks, 2 and 6 months, 3 and 5 years after transplantation • eGFR according to MDRD-IV, CKD-EPI, Nankivell 5 days, 4 weeks, 2 and 6 months, 3 and 5 years after transplantation • delayed graft function • rate of chronic-humoral rejections • rate of donor specific Anti-human leukocyte antigen (HLA) antibodies six months after transplantation and during follow up • changes in histology • dose modification of Advagraf® Safety • New Onset Diabetes mellitus after transplantation • bacterial or viral Infections • polyomavirus infection, in particular PCR positive polyomavirus infection requiring treatment • adverse events (within 6 months) • follow up complications (month 7 to 5 year follow up visit)
Number of patients	planned sample size: 400 (360 evaluable patients plus 10% drop out) patients screened: 737 patients enrolled: 432 patients analysed: 398
Studied period	First patient in: 15.11.2014 Last patient in: 17.07.2018 Last patient last visit: 10.11.2023
Inclusion criteria	1. Male or female allograft recipients at least 18 years old 2. Primary or secondary kidney transplantation 3. Deceased or living donor 4. Normal immunological risk profile,

	• PRA level ≤ 20%, • AB0-comaptible donation, • negative crossmatch 5. Written informed consent of the patient 6. Allowance to contact the families doctor and/or nephrologist for study relevant data
Exclusion criteria	1. Former graft loss due to severe rejection within the first year after transplantation (in case of secondary transplantation) 2. Multiorgan recipient 3. Patients receiving a kidney from a „non heart beating“ donor 4. Complete HLA-identical living donor (twins) 5. Patients with a history of malignancy during the last five years (except squamous or basal cell carcinoma of the skin after successful treatment) 6. Patients with uncontrolled infectious disease, particularly patients who are HIV positive or suffer from chronic hepatitis B or C or tuberculosis 7. Patients with severe gastroenteric disorder, particularly severe diarrhoea and symptoms of enteric malabsorption 8. Patients suffering from liver cirrhosis Child B or C or other severe liver disease (ASAT, ALAT, GammaGT ≥ 3-fold increased) 9. Thrombopenia < 70.000/mm^3 10. Leukopenia < 2.500/mm^3 11. Participation in another clinical trial within the last 4 weeks prior to inclusion 12. Addiction or other disorders that do not allow the person concerned, to estimate the nature, scope and possible consequences of the clinical trial 13. Pregnant or breast feeding women 14. Women of childbearing age, except women who meet any of the following criteria: - post-menopausal (12 months natural amenorrhea or 6 months amenorrhea with serum > 40 U/ml) - postoperatively (6 weeks after bilateral ovarectomy with or without hysterectomy) - regular and correct use of a contraceptive method with error rate < 1% per year (e.g. implants, depot injections, oral contraceptives, intrauterine device); - sexual abstinence - vasectomy of the partner 15. Evidence that the patient is likely to fail to comply with the protocol (e.g. lack of cooperation) 16. Hypersensitivity to tacrolimus or any other ingredient listed in the product information as well as to other macrolides

Test product	Advagraf® Dose of administration: dose see below, administered once per day Mode of administration: oral use Batch number(s): In this study, trial medication was taken from clinical stocks. Each trial site used the medication that was available on site. Hence, no batch numbers are provided in this report.
Reference therapy	not applicable
Duration of treatment	Treatment arm "Standard Care" Product: Advagraf® Dose: preoperative at day of transplantation: 1x0,2 mg/kg BW day 1 (first day after transplantation): 1x0,2 mg/kg BW day 2 to 6: tacrolimus trough levels of 7-9 ng/ml day 7 to 60: tacrolimus trough levels of 7-9 ng/ml day 61 to 180: tacrolimus trough levels of 6-8 ng/ml Duration: day 0 to 180 Treatment arm "Slow and Low" Product: Advagraf® Dose: preoperative at day of transplantation: 1 x 5 mg day 1 (first day after transplantation): 1 x 5 mg day 2 to 6: 1 x 5 mg day 7 to 60: tacrolimus trough levels of 5-7 ng/ml day 61 to 180: tacrolimus trough levels of 4-6 ng/ml Duration: day 0 to 180

2 INDIVIDUAL STUDY TABLE

Not applicable.

3 INVESTIGATORS AND TRIAL SITES

No. of Trial Site	Trial Site	Investigator(s)
1	Universitätsklinikum Dresden Medizinische Klinik III Fetscherstr. 74 01307 Dresden	Prof. Dr. med. Christian Hugo
2	Charité Universitätsmedizin Berlin Campus Virchow-Klinikum Medizinische Klinik mit Schwerpunkt Nephrologie und internistische Intensivmedizin Augustenburger Platz 113353 Berlin	Prof. Dr. med. Petra Reinke

No. of Trial Site	Trial Site	Investigator(s)
3	Charité - Universitätsmedizin Berlin Campus Charité Mitte Medizinische Klinik mit Schwerpunkt Nephrologie Charitéplatz 1 10117 Berlin	Prof. Dr. med. Klemens Budde
4	Universitätsklinikum Knappschaftskrankenhaus Bochum GmbH Chirurgische Universitätsklinik In der Schornau 23-25 44892 Bochum	Dr. med. Peter Schenker
5	Rheinische Friedrich-Wilhelms-Universität Bonn Universitätsklinikum Bonn (AöR) Medizinische Klinik und Poliklinik I Sigmund-Freud-Str. 25 53105 Bonn	Prof. Dr. med. Rainer Peter Woitas
6	Universitätsklinikum Erlangen Medizinische Klinik IV Nephrologie und Hypertensiologie Ulmenweg 18 91054 Erlangen	Prof. Dr. med. Michael Wiesener
7	Universitätsklinikum Essen Klinik für Nephrologie Hufelandstr. 55 45122 Essen	Prof. Dr. med. Oliver Witzke
9	Universitätsklinikum Halle/Saale Innere Medizin II Arbeitsbereich Nephrologie/Hypertensiologie Ernst-Grube-Str. 40 06120 Halle (Saale)	Prof. Dr. med. Matthias Girndt
11	Medizinische Hochschule Hannover Klinik für Nieren- und Hochdruckerkrankungen Carl-Neuburg-Straße 1 30625 Hannover	Prof. Dr. med. Hermann Haller
12	Nierenzentrum Heidelberg Im Neuenheimer Feld 162 69120 Heidelberg	Prof. Dr. med. Claudia Sommerer
13	Universität des Saarlandes Klinik für Innere Medizin IV Gebäude 40 Kirrberger Straße 66421 Homburg/Saar	Prof. Dr. med. Urban Sester

No. of Trial Site	Trial Site	Investigator(s)
14	Universitätsklinikum Jena Klinik für Innere Medizin III, Nephrologie Erlanger Allee 101 07747 Jena	Prof. Dr. med. Gunter Wolf
15	Universitätsklinikum Köln (AöR) Klinik II für Nephrologie, Rheumatologie, Diabetologie und Allgemeine Innere Medizin Kerpener Straße 62 50937 Köln	Prof. Dr. med. Christine Kurschat
16	Kliniken der Stadt Köln gGmbH Medizinische Klinik I Ostmerheimer Str. 200 51109 Köln	Dr. med. Wolfgang Arns
17	Universität Leipzig Medizinische Fakultät Klinik und Poliklinik für Viszeral-, Transplantations-, Thorax und Gefäßchirurgie Liebigstr. 20 04103 Leipzig	Prof. Dr. med. Daniel Seehofer
18	Universitätsmedizin der Johannes Gutenberg-Universität Mainz I. Medizinische Klinik und Poliklinik Langenbeckstraße 1 55131 Mainz	Dr. med. Julia Weinmann-Menke
19	Universitätsmedizin Mannheim V Medizinische Klinik / Nephrologie Theodor-Kutzer-Ufer 1-3 68167 Mannheim	Prof. Dr. med. Bernd Krüger
20	Universitätsklinikum der WWU Münster Klinik für Allgemein- und Viszeralchirugie , Transplantationszentrum Albert- Schweitzer- Campus 1 48149 Münster	Dr. med. Thomas Vogel
21	Universitätsklinikum Würzburg Nephrologie der Medizinischen Klinik und Poliklinik I Oberdürrbacher Str. 6 97080 Würzburg	Dr. med. Anna Laura Herzog

Table **1** Investigators and Trial Sites

4 METHODOLOGY

The “Slow and Low” trial was an investigator-initiated, prospective, randomized, open-label, multicenter study with two parallel study arms of adult renal transplant recipients in fourteen German centers (EudraCT-Nr: 2013-001770-19). All patients provided written informed consent and were allowed to withdraw from the study at any time. Demographic and baseline data of the recipients and donors were assessed before transplantation including serological-status for cytomegalovirus (CMV) and Epstein Barr virus (EBV). Documentation of clinical signs, laboratory data, adverse events, and efficacy data were obtained at baseline, day 6, and at months 1, 2, and 6. Follow up visits were performed 3 and 5 years after transplantation.

Participants were centrally randomly assigned via a web-based randomization algorithm in a 1:1 ratio after signing informed consent before transplantation. The allocation list was computer-generated by block randomization with blocks of length four using nQuery-Advisor® 6.01 and stratified by trial site, living donation, and transplantation via European Senior Program (ESP). The randomization algorithm was incorporated in the electronic data management system and after obtaining informed consent the trial sites were allowed to request a patient’s randomization result.

Patients were randomized to one of two study arms, see Figure **1**.

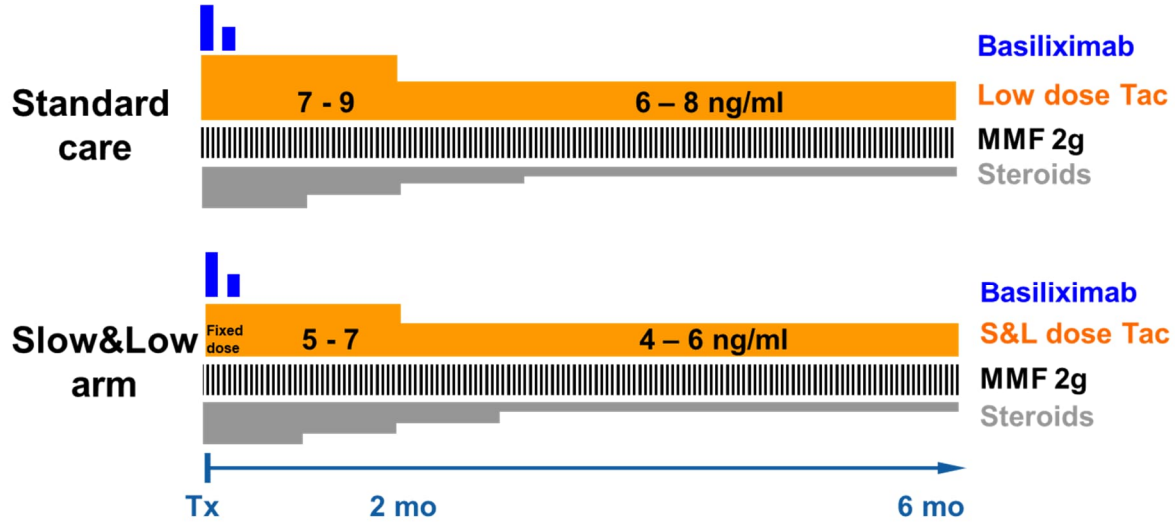

Figure **1** Treatment arms

All patients received induction therapy with basiliximab (Simulect®, Novartis, 20 mg intravenously on day 0 before allograft reperfusion and day 4), prolonged release tacrolimus administered once daily (Advagraf®, Astellas Pharma GmbH), 2 x 1 g per day mycophenolate mofetil (MMF) (CellCept®, Roche Pharma AG), or enteric coated mycophenolic sodium (EC-MPS) at equivalent doses, and prednisolone (Solu Decortin®, Merck Serono), all of which were started before transplantation. Prednisolone/Methylprednisolone was given at center standard, but tapering had to be done to reach 20 mg/16 mg after four weeks, 10 mg/8 mg after eight weeks, and 5 mg/4 mg daily after 12 weeks, respectively.

In the Standard Care arm, tacrolimus starting dose was 0·2 mg/kg bodyweight once daily (as recommended in the product information) at day 0 and 1 followed by tacrolimus trough levels of 7-9 ng/ml in the first two months and 6-8 ng/ml from month 3 to 6. Trough levels until day 6 had to be determined on a daily basis and later according to center standard.

In the Slow & Low arm, prolonged release tacrolimus was started once daily at a fixed dose of 5 mg before and for the first six days after transplantation. Trough levels until day 6 had to be determined on a daily basis but were blinded to the investigators. The first unblinded tacrolimus trough level on day 6 led to the first dose correction on day 7 by the investigators. From day 7 on, tacrolimus trough levels were adapted to reduced levels of 5-7 ng/ml in the first two months and 4-6 ng/ml from month 3 to 6. For the event of reaching a potentially toxic tacrolimus drug level of 20 µg/ml or higher on two days, a specific surveillance system was implemented to unblind and inform the investigators for correction of the fixed 5 mg dose of tacrolimus.

External monitoring was performed throughout the study period. An independent data safety monitoring board consisting of two international transplant physicians and one statistician evaluated overall study safety after inclusion of 40, 80, and 200 patients. Interim analyses of the primary objective, i.e. primary endpoint, were neither planned nor performed.

5 STATISTICAL METHODS

The final analysis was planned in detail in two statistical analysis plans (confirmatory analysis of primary endpoint: version 3.0F as of 31st January 2020; updated SAP for follow up analysis: version 4.0F as of 30th October 2024). Here, only the most important specifications are presented.

The study was planned with a significance level of 5 percent and a power of 90 percent was aimed at. No interim analysis of efficacy was planned. In the confirmatory analysis, one statistical test was performed in one analysis population, namely ITT population. Thus, no type-one-error adjustment was required.

Analysis Populations:

- Intent-to-treat population (ITT) consists of all randomized patients who gave written informed consent, received at least one dose of the investigational medical product (IMP, Advagraf®), and underwent successful renal transplantation.
- Per-protocol set (PPS) consists of all patients of the ITT population without any severe protocol deviation. Severe protocol deviations were
  - violation of inclusion or exclusion criteria
  - Advagraf® discontinued and not followed by any other treatment with tacrolimus (Prograf, generic medicinal product)
  - induction therapy with basiliximab:
    - less than two doses
    - two doses not applied between day -1 and 14 (day 0 = day of transplantation)
  - steroids discontinued within 5 months after transplantation
  - administration of MMF/CellCept
    - interrupted for consecutive 22 days or longer
    - dose reduced below 2 x 500 mg CellCept or 2 x 360 mg Myfortic for 22 consecutive days or longer
  - additional immunosuppression to the 3-fold combination predefined in the protocol

  Any exception regarding immunosuppressive treatment defined in the study protocol were taken into consideration.
- Safety analysis set identical to ITT.

Confirmatory analysis of primary endpoint (ITT): The primary endpoint was the combined endpoint of the incidence of BPAR including borderline rejection, graft loss, and death within the first 6 months after renal transplantation. Absolute and relative frequencies of primary endpoint for evaluable patients were reported by treatment arm. Non-inferiority of treatment "Slow and Low" was investigated by a so-called superiority test (one sided test of equivalence) with 12.5 % as superiority margin for the difference of primary endpoint in treatment arms (arm „slow and low" minus arm „standard care"). The upper limit of the one-sided 95 percent confidence level of the difference was of interest which is equivalent to the upper limit of the two-sided 90 percent confidence interval.

A patient was not evaluable if the observational period was stopped before day 152 without preceding event. The frequency was described within each treatment arm. No imputation of missing primary endpoint was performed.

Sensitivity analyses of primary endpoint (ITT, PPS):

i. per protocol analysis of primary endpoint analogous to ITT analysis
ii. multivariable analysis to adjust for risk factors
iii. event rate of primary endpoint estimated by Kaplan Meier method
iv. primary endpoint excluding borderline rejection
v. primary endpoint not counting rejections detected by protocol biopsies
vi. primary endpoint excluding borderline rejection detected by protocol biopsy

Absolute and relative frequencies by treatment arm along with 90 percent two-sided confidence interval.

Investigation of center effects:

- description of primary endpoint by trial site (trial sites with less than 10 evaluable patients will be combined in one group)
- visualization of results by Forest Plot
- test for heterogeneity

Follow up analysis of primary endpoint (ITT, PPS):

i. one, three and five year event rates estimated by Kaplan Meier method
ii. no non-inferiority test as no non-inferiority margin was pre-specified for these rates
iii. multivariable cox regression analysis to adjust for risk factors.

Secondary endpoints of efficacy:

<u>Creatinine and eGFR (ITT, PPS):</u>

Estimated GFR was calculated according to MDRD-IV (Levey et al. 2006), CKD-EPI (Levey et al. 2009), and Nankivell (Nankivell et al. 1995). The course of the parameters was described by median and IQR for each treatment arm and visit. Boxplots were presented. These descriptions were based on reported values, i.e. no imputed values were used. Additionally, missing values not caused by graft loss or death were imputed by fully conditional specification regression method (Brand 1999; van Buuren 2007) accounting for sex, age (age of recipient, age of donor; or ECD), kind of donation (living or postmortem), and reported creatinine values once with and once without study arm. Courses of laboratory values were analyzed by linear mixed models with patient as random factor.

<u>Delayed graft function (ITT, PPS):</u>

Definition of DGF

- assessed by investigator at trial site or

- defined as need for dialysis after transplantation, i.e. at least one dialysis within 4 days after TX followed by at least one other dialysis until day 7. The need for dialysis must not be caused by graft rejection or graft loss.

- absolute and relative frequencies of patients with delayed graft function by treatment arm and in total
- Fisher's exact test to test for differences between the treatment arms.

Rate of donor specific Anti-human leukocyte antigen (HLA) antibodies (ITT, PPS):

- description of evaluable cases, i.e. patients with documented investigation of Anti-HLA antibodies
- absolute and relative frequencies by treatment arm and in total
- Fisher's exact test

Changes in histology - IFTA, BKV-nephropathy, relapse (ITT, PPS):

- absolute and relative frequencies of patients by treatment arm and in total
- Fisher's exact test or Chi-square test to test for differences between the treatment arms

Secondary endpoint – Dose modification of Advagraf® (ITT, PPS):

- description by mean and SD as well as median and IQR
- tested by t-test for independent groups or Mann-Whitney-U-test, as appropriate (after inspection of distribution)

Secondary endpoints of safety:

New Onset Diabetes mellitus after transplantation (ITT, PPS):

- analysis restricted to patients without pre-existing diabetes mellitus
- absolute and relative frequencies of patients by treatment arm and in total
- Kaplan Meier estimates and log-rank test to investigate time from transplantation to new onset diabetes mellitus and to estimate event rates

Sensitivity analysis: occurrence of NODAT at visit 3 (day 28) or later. Investigated by same methods.

Adverse Events (ITT):

- absolute and relative frequency of patients with AE, AR, SAE, SAR, SUSAR
- Chi-square test or Fishers exact test, as appropriate.
- absolute and relative frequency of serious cardiovascular events (e.g. myocardial infarction, catheter intervention, stroke, peripheral ischemia) by treatment arm

Frequency of bacterial or viral infection, BKV infection, Complications during FU (ITT):

- absolute and relative frequency of patients
- Chi-square test or Fishers exact test, as appropriate.

Subgroup analyses:

- Living donation
- Postmortem donation
- both, donor and recipient >= 65 years
- donor < 65 years or recipient < 65 years
- donors with expanded criteria
- all values of tacrolimus level in the pre-specified target range

- low variability of tacrolimus level (lower third, variability calculated for day 29 to 180)
- intermediate variability of tacrolimus level (middle third, variability calculated for day 29 to 180)
- high variability of tacrolimus level (upper third, variability calculated for day 29 to 180)

No non-inferiority margin was defined for subgroups or sensitivity analyses. Therefore, no test was performed.

6 RESULTS

Patients were recruited from November 15th, 2014 to July 17th, 2018 in 14 German trial sites. 737 patients were screened. Among these, 432 patients were eligible and randomized before transplantation. 34 patients were excluded from intent to treat population due to several reasons, see Consort flow chart in Figure **2**, leading to 398 patients in the ITT population.

6.1 ANALYSIS POPULATIONS

Intent to treat population comprises 398 patients. 385 (96·7%) were analysed for primary endpoint. These 13 patients prematurely terminated the trial before month 6 without having an event in the combined primary endpoint. 83 patients with severe protocol deviations were excluded from per protocol set (for reasons see consort flow diagram Figure **2**).

6.2 CONSORT FLOW DIAGRAM

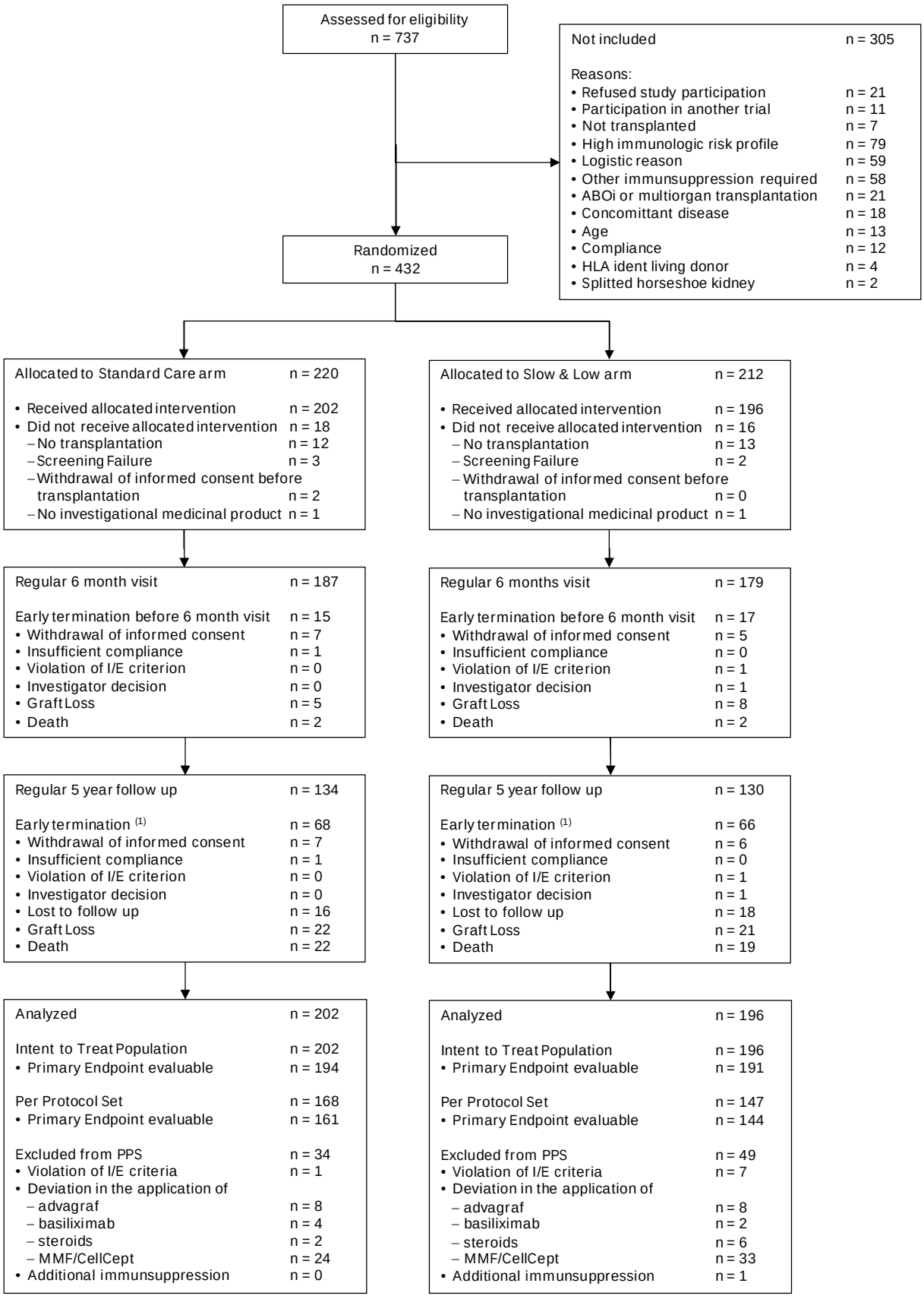

Figure **2** CONSORT flow diagram
(1) including reasons for early termination before 6 month visit

6.3 BASELINE CHARACTERISTICS

Baseline characteristics of the study arms were well balanced and did not differ among both groups, see table below. Mean age of study population was 55 years and two thirds of the patients were male. Panel-reactive antibodies were found in 15 patients only. Six of them were randomized to the Control arm and nine of them to the Slow & Low arm.

	Standard Care Arm	**Slow & Low Arm**	**Total**
	N = 202	**N = 196**	**N = 398**
Recipient age [years]	54 ± 13	55 ± 12	55 ± 13
Recipient age ≥ 65 years [(n (%)]	55 (27·2 %)	50 (25·5 %)	105 (26·4 %)
Male sex [n (%)]	131 (64·9 %)	128 (65·3 %)	259 (65·1 %)
Body mass index [kg/m^2]	26·5 ± 4·2	27·2 ± 4·8	26·8 ± 4·5
Cause of end-stage renal disease			
Glomerulonephritis [n (%)]	61 (30·2 %)	68 (34·7 %)	129 (32·4 %)
Diabetes mellitus [n (%)]	17 (8·4 %)	14 (7·1 %)	31 (7·8 %)
Arterial hypertension [n (%)]	17 (8·4 %)	16 (8·2 %)	33 (8·3 %)
Pyelonephritis or Interstitial nephritis [n (%)]	10 (5·0 %)	8 (4·1 %)	18 (4·5 %)
Cystic or polycystic kidney disease [n (%)]	38 (18·8 %)	25 (12·8 %)	63 (15·8 %)
Systemic autoimmune diseases(1) [n (%)]	5 (2·5 %)	6 (3·0 %)	11 (2·8 %)
Reflux nephropathy [n (%)]	6 (3·0 %)	4 (2·0 %)	10 (2·5 %)
Other(2) [n (%)]	48 (23·8 %)	55 (28·1 %)	103 (25·9 %)
Medical history			
Diabetes mellitus [n (%)]	34 (16·8 %)	30 (15·3 %)	64 (16·1 %)
Arterial hypertension [n (%)]	192 (95·0 %)	190 (96·9 %)	382 (96·0 %)
Coronary heart disease [n (%)]	51 (25·2 %)	47 (24·0 %)	98 (24·6 %)
Cerebrovascular disease [n (%)]	6 (3·0 %)	6 (3·1 %)	12 (3·0 %)
Peripheral arterial disease [n (%)]	19 (9·4 %)	15 (7·7 %)	34 (8·5 %)
Heart Failure [n (%)]	38 (18·8 %)	18 (9·2 %)	56 (14·1 %)
Asthma or COPD [n (%)]	10 (5·0 %)	16 (8·2 %)	26 (6·5 %)
Malignancy [n (%)]	8 (4·0 %)	22 (11·2 %)	30 (7·5 %)
Dialysis waiting time of recipients [months]	73·3 ± 43·9	71·8 ± 45·5	72·6 ± 44·6
Type of donor			

	Standard Care Arm	Slow & Low Arm	Total
	N = 202	N = 196	N = 398
Deceased [n (%)]	167 (82·7 %)	163 (83·2 %)	330 (82·9 %)
Living [n (%)]	35 (17·3 %)	33 (16·8 %)	68 (17·1 %)
Donor with expanded criteria [n (%)]	105 (52·0 %)	107 (54·6 %)	212 (53·3 %)
Donor age (years)	56 ± 14	57 ± 12	56 ± 13
Donor age ≥ 65 years [n (%)]	56 (27·7 %)	52 (26·5 %)	108 (27·1 %)
Number of antigen mismatches: A, B, and DR	3·0 ± 1·7	2·9 ± 1·7	3·0 ± 1·7
Panel-reactive antibodies before transplantation [n (%)]	196 (97·0 %)	187 (95·4 %)	383 (96·2 %)
Previous transplants [n (%)]	11 (5·4 %)	4 (2·0 %)	15 (3·8 %)
Cold-ischaemia time of deceased donor grafts (min)	703·4 ± 230·5	719·3 ± 243·1	711·3 ± 236·6
Cytomegalovirus serologic status			
Missing [n (%)]	8 (4·0 %)	6 (3·1 %)	14 (3·5 %)
donor negative, recipient negative (low risk) [n (%)]	31 (15·3 %)	43 (21·9 %)	74 (18·6 %)
donor positive/negative, recipient positive (intermediate risk) [n (%)]	99 (49·0 %)	92 (46·9 %)	191 (48·0 %)
donor positive, recipient negative (high risk) [n (%)]	64 (31·7 %)	55 (28·1 %)	119 (29·9 %)
Epstein-Barr virus serological status			
Missing [n (%)]	23 (11·4 %)	16 (8·2 %)	39 (9·8 %)
donor negative, recipient negative (low risk) [n (%)]	1 (0·5 %)	1 (0·5 %)	2 (0·5 %)
donor positive/negative, recipient positive (intermediate risk) [n (%)]	170 (84·2 %)	173 (88·3 %)	343 (86·2 %)
donor positive, recipient negative (high risk) [n (%)]	8 (4·0 %)	6 (3·1 %)	14 (3·5 %)

Data are presented as mean ± standard deviation, or absolute and relative frequencies.
(1) comprises vasculitis, systemic lupus erythematosus, and hemolytic uremic syndrome·
(2) comprises drug induced nephropathy, unkown etiology and other reasons.

Table **2** Baseline Characteristics

6.4 STUDY TREATMENT AND COMPLIANCE

All patients were treated by Advagraf®. A short description of dosing is provided in the next table. In 16 patients (4.0%), Advagraf® was discontinued and not followed by any other

treatment with tacrolimus (standard care arm 8 patients, slow and low arm 8 patients) during the first 6 months. These patients were excluded from per protocol set.

	Standard Care Arm	**Slow & Low Arm**
	N = 202	**N = 196**
Mean daily dose of Advagraf® [mg]		
week 1	11·4 ± 3·6	5·2 ± 1·4
week 2	10·4 ± 4·4	7·8 ± 3·6
week 3	10·5 ± 4·8	9·2 ± 4·6
week 4	9·7 ± 4·9	8·7 ± 4·4
month 2	8·0 ± 3·9	7·1 ± 3·7
month 3	6·5 ± 3·4	5·9 ± 3·0
month 4	5·9 ± 3·3	5·4 ± 3·2
month 5	5·8 ± 3·2	5·1 ± 3·2
month 6	5·6 ± 3·2	4·9 ± 3·1
Data are presented as mean ± standard deviation.		

Table **3** Administration of Advagraf®

Target trough levels for tacrolimus were within the predefined therapeutic window in the Standard Care arm but only during the first month in the Slow & Low arm (see Figure **3**), thereafter tacrolimus trough levels became more overlapping with the Standard Care arm. One patient had to be intervened for adaption of the fixed dose approach as predefined by tacrolimus trough levels twice > 20 µg/ml during that period.

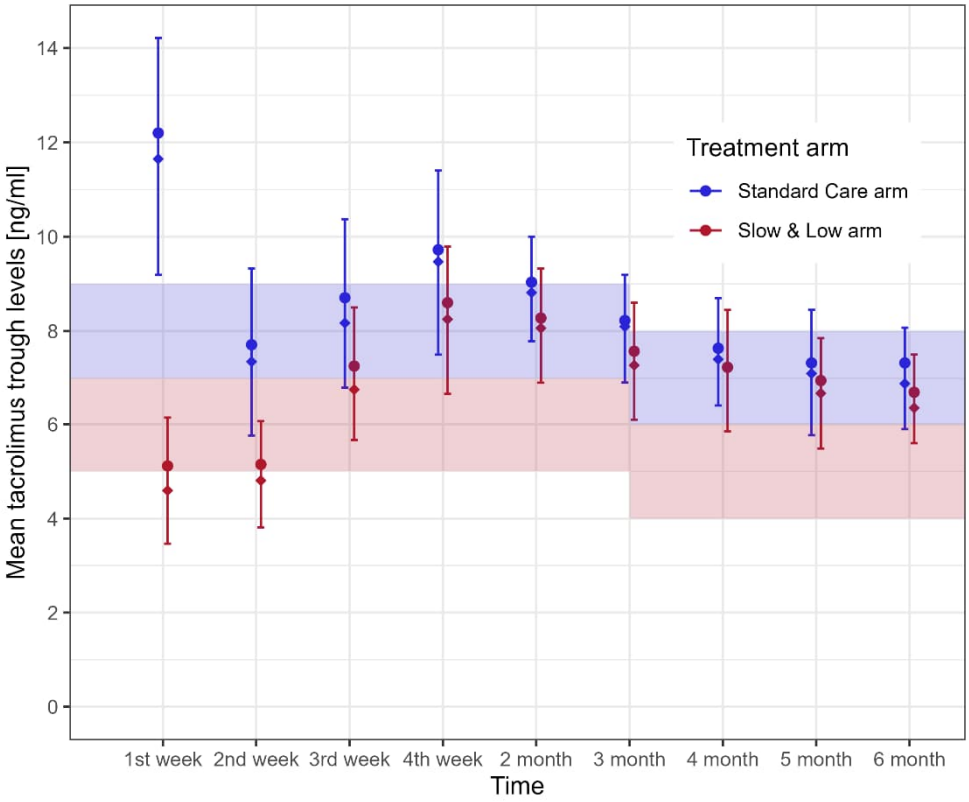

Figure **3** Mean tacrolimus trough level

Mean tacrolimus trough levels during different time periods after renal transplantation. In case, more than one measurement per patient was documented, mean tacrolimus trough level per period was calculated. The coloured highlighted areas show the target ranges of the corresponding treatment arms over time. Filled diamond = median, filled circle = mean, strokes = interquartile range.

6.5 PRIMARY ENDPOINT

6.5.1 Confirmatory Analysis in ITT Population

At 6 months, the incidence of the combined primary endpoint BPAR (including borderline rejection), graft loss, and death was evaluable in 385 of 398 patients and was similar among both study arms.

	Standard Care Arm	**Slow & Low Arm**	**Treatment Effect [5] and 90% or 95% CI**	**p-value**
	N = 202	**N = 196**		
Primary Endpoint[1]				
BPAR, Graft Loss or Death [$n/n_{evaluable}$ (%)] at 6 months	40 / 194 (20·6%)	42 / 191 (22·0%)	1·4 [-5·5; 8·3]	0·004 [2]
Events in primary Endpoint [3] [n (%)]				
BPAR, thereof	32 (16·5%)	33 (17·3%)		
Antibody-mediated rejection	12 (6·2%)	13 (6·8 %)		

	Standard Care Arm	Slow & Low Arm	Treatment Effect (5) and 90% or 95% CI	p-value
	N = 202	N = 196		
Acute antibody-mediated rejection Grade I	2 (1·0 %)	8 (4·2 %)		
Acute antibody-mediated rejection Grade II	9 (4·6 %)	5 (2·6 %)		
Acute antibody-mediated rejection Grade III	1 (0·5 %)	0 (0·0 %)		
Chronic active humoral rejections	2 (1·0 %)	0 (0·0 %)	-1·0 [-2·5; 0·4]	0·499 (4)
Borderline Rejection	22 (11·3 %)	12 (6·3 %)		
T-cell-mediated rejection	10 (5·2 %)	22 (11·5 %)	6·4 [0·9;11·9]	0·027 (4)
Acute T-cell-mediated rejection Grade IA	2 (1·0 %)	11 (5·8 %)		
Acute T-cell-mediated rejection Grade IB	0 (0·0 %)	2 (1·0 %)		
Acute T-cell-mediated rejection Grade IIA	4 (2·1 %)	5 (2·6 %)		
Acute T-cell-mediated rejection Grade IIB	3 (1·5 %)	1 (0·5 %)		
Acute T-cell-mediated rejection Grade III	1 (0·5 %)	3 (1·6 %)		
Chronic active T-cell mediated rejection	1 (0·5 %)	2 (1·0 %)		
Graft Loss	5 (2·6 %)	7 (3·7 %)		
Death	4 (2·1 %)	2 (1·0 %)		

(1) Compared to the analysis of the first part of the study (Stumpf et al. 2024), 2 additional patients were evaluable in the follow up analysis, one per arm. Neither of them had an event.
(2) Non-inferiority test with non-inferiority margin 12·5 %
(3) Multiple answers possible
(4) Fisher's exact test (two-sided)
(5) Treatment effect calculated as absolute risk difference between Slow & Low arm and Standard Care arm for categorical data. Two-sided 90 percent confidence interval for primary endpoint, otherwise, two-sided 95% confidence interval.

Table **4** Primary endpoint in ITT population

The non-inferiority criteria was met with a difference of 1·4 % and a two-sided 90 percent confidence interval from -5·5 % to 8·3 %. The p-value of 0·004 of the one-sided test of equivalence with a non-inferiority margin of 12·5 percent demonstrated non-inferiority.

6.5.2 Primary Endpoint in Per Protocol Set

	Standard Care Arm	Slow & Low Arm	Treatment Effect and 90% CI	p-value
	N = 168	N = 147		
Primary Endpoint(1)				
BPAR, Graft Loss or Death [$n/n_{evaluable}$ (%)] at 6 months	30 / 161 (18·6%)	29 / 144 (20·1%)	1·5 [-6·0; 9·0]	0·008 (2)

(1) Compared to the analysis of the first part of the study (Stumpf et al. 2024), 2 additional patients were evaluable in the follow up analysis, one per arm. Neither of them had an event.
(2) Non-inferiority test with non-inferiority margin 12·5 %

Table **5** Primary endpoint in per protocol set

Non-inferiority was also reached in the per protocol set.

6.5.3 Sensitivity and Subgroup Analyses of Primary Endpoint

Study or Subgroup	Slow & Low Events	Slow & Low Total	Standard Care Events	Standard Care Total	Risk Difference M-H, Fixed, 90% CI
01 Intent to Treat Population	42	191	40	194	0.0137 [-0.0549, 0.0824]
02 ITT not counting borderline rejection	32	190	27	194	0.0292 [-0.0313, 0.0898]
03 ITT not counting rejection by protocol biopsy	41	191	34	194	0.0394 [-0.0270, 0.1058]
04 ITTnot counting borderline by protocol biopsy	42	191	35	194	0.0395 [-0.0275, 0.1065]
05 Living donor	10	33	7	34	0.0971 [-0.0770, 0.2713]
06 Postmortem Donation	32	158	33	160	-0.0037 [-0.0781, 0.0707]
07 European Senior Program	6	37	11	42	-0.0997 [-0.2494, 0.0499]
08 both, donor and recipient 65 yrs or older	6	38	11	42	-0.1040 [-0.2521, 0.0440]
09 donor or recipient younger than 65 yrs	36	153	29	152	0.0445 [-0.0325, 0.1215]
10 Expanded Criteria Donor	26	102	25	100	0.0049 [-0.0956, 0.1055]
11 Low Variability of Tacrolimus Metabolism Rate	8	52	11	56	-0.0426 [-0.1626, 0.0774]
12 Intermediate Var. of Tacrolimus Metabolism Rate	14	70	8	55	0.0545 [-0.0564, 0.1654]
13 High Variability of Tacrolimus Metabolism Rate	7	53	14	71	-0.0651 [-0.1741, 0.0439]
14 Per Protocol Set	29	144	30	161	0.0151 [-0.0596, 0.0897]

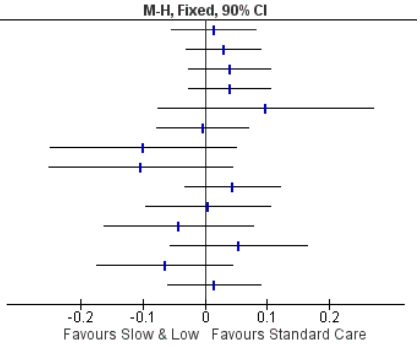

Figure **4** Sensitivity and subgroup analyses of primary endpoint

Figure **4** presents risk differences in different populations (intent to treat, per protocol set), in various sensitivity analyses (counting of events: excluding borderline rejections or rejections detected in protocol biopsies), or subgroups.

The non-inferiority criterion defined for intent-to-treat population is not met if the upper limit of the 90 percent two-sided confidence interval is higher than 0·1250.

For sensitivity analyses and subgroups, no non-inferiority criterion was predefined.

6.5.4 Follow Up Analysis of Primary Endpoint in ITT

The combined endpoint was observed until the last study visit 5 years after transplantation. A median observation time of 60 months was reached in the whole study population. Two patients are not included in the analysis as they stopped the study right after transplantation and, therefore, neither endpoint data nor censoring time points were available.

In total, 141 patients with events were reported (standard care arm 71 events, slow and low arm 70 events). Details on events are provided in table 6.

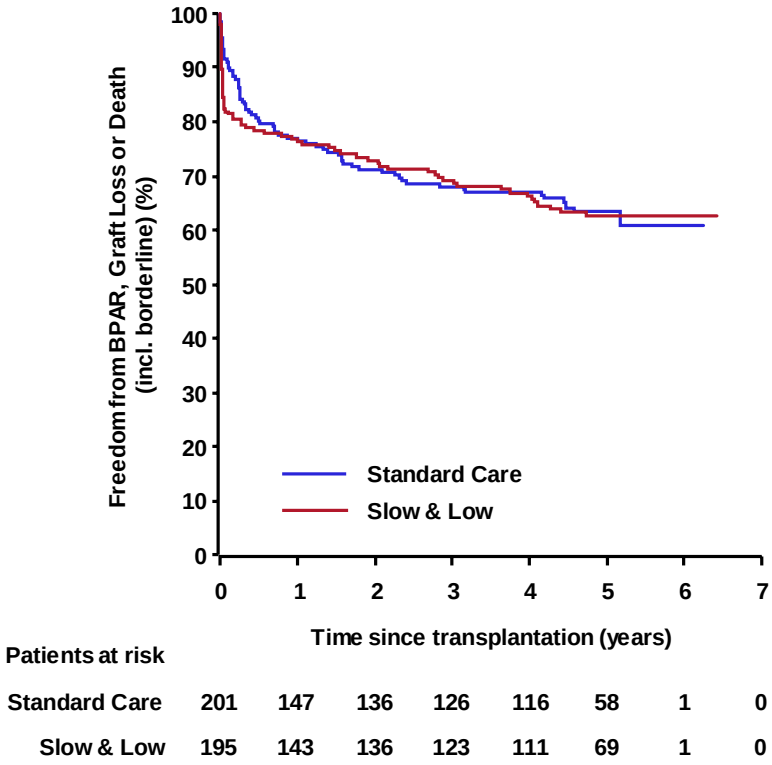

Figure **5** Kaplan Meier plot of primary endpoint

	Standard Care Arm	**Slow & Low Arm**
	N = 202	**N = 196**
Events reported [1] [n (%)]		
BPAR, thereof	41 (20·4%)	41 (21·0%)
Antibody-mediated rejection	18 (9·0%)	19 (9·7%)
Acute antibody-mediated rejection Grade I	5 (2·5%)	10 (5·1%)
Acute antibody-mediated rejection Grade II	12 (6·0%)	6 (3·1%)
Acute antibody-mediated rejection Grade III	1 (0·5%)	1 (0·5%)
Chronic active humoral rejections	3 (1·5%)	2 (1·0%)
Borderline Rejection	25 (12·4%)	15 (7·7%)
T-cell-mediated rejection	14 (7·0%)	25 (12·8%)
Acute T-cell-mediated rejection Grade IA	3 (1·5%)	13 (6·7%)
Acute T-cell-mediated rejection Grade IB	0 (0·0%)	2 (1·0%)
Acute T-cell-mediated rejection Grade IIA	6 (3·0%)	5 (2·6%)
Acute T-cell-mediated rejection Grade IIB	3 (1·5%)	1 (0·5%)
Acute T-cell-mediated rejection Grade III	1 (0·5%)	3 (1·5%)
Chronic active T-cell mediated rejection	3 (1·5%)	3 (1·5%)

	Standard Care Arm	Slow & Low Arm
	N = 202	N = 196
Graft Loss	11 (5·5%)	13 (6·7%)
Death	21 (10·4%)	17 (8·7%)
(1) multiple answers possible		

Table **6** Follow Up of primary endpoint in ITT population

Results in per protocol set are comparable (patients with events: 53 out of 167 in standard care arm and 46 out of 146 in slow and low arm).

6.5.5 Graft Survival

Additionally, graft survival counting graft loss and death as events (both components of the primary endpoint) was investigated. Events reported are comparable (standard care arm: 22 graft losses and 22 deaths; slow and low arm: 21 graft losses and 19 deaths).

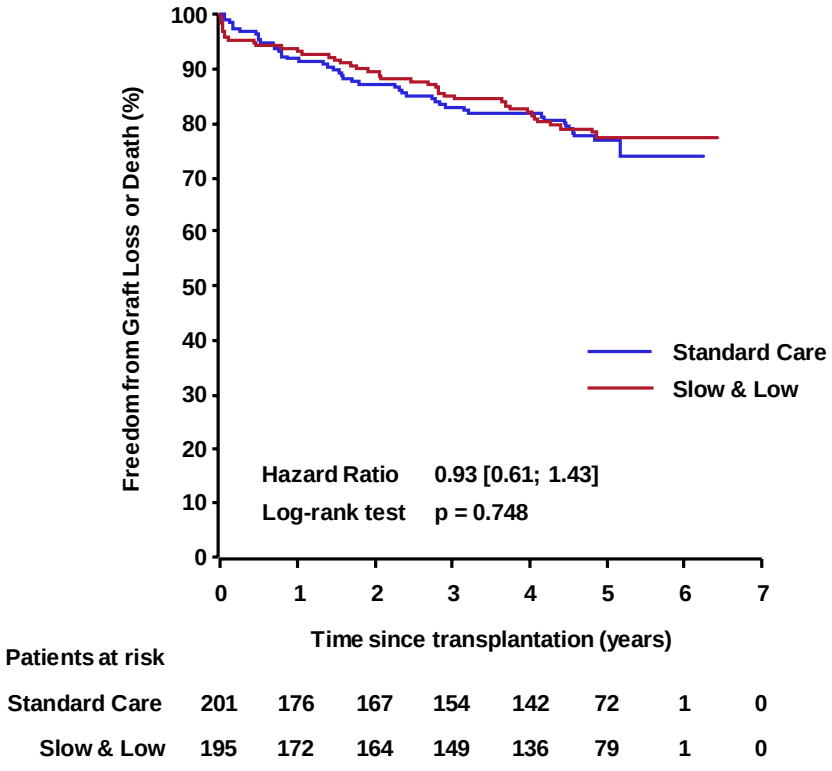

Figure **6** Kaplan Meier plot of graft survival

6.6 SECONDARY ENDPOINTS OF EFFICACY

6.6.1 Course of Serum Creatinine

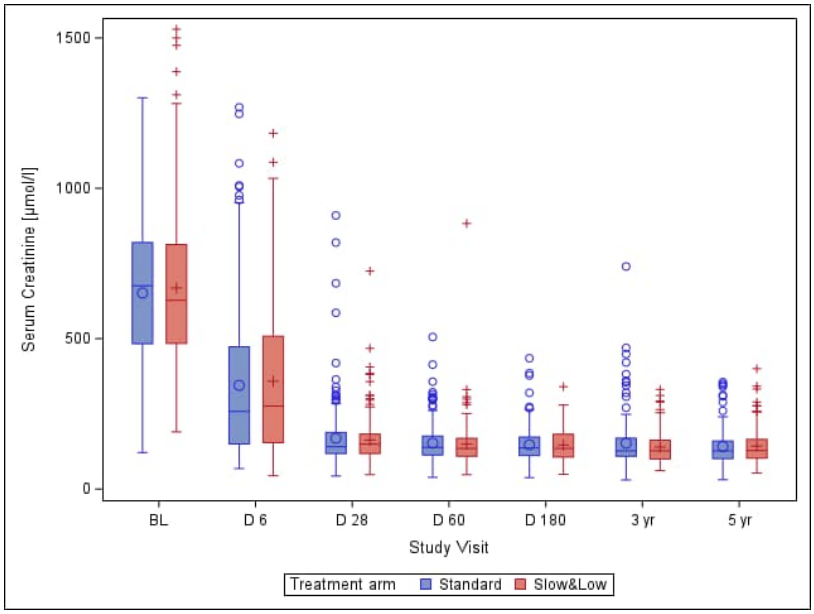

Figure **7** Course of serum creatinine

Serum Creatinine shows a similar course in both groups. In a mixed model for logarithmized serum creatinine values with patient as random effect, no statistically significant treatment effect was observed (F=0.00; p=0.960). Several imputation methods for missing values show similar results.

6.6.2 Course of eGFR according to MDRD-IV

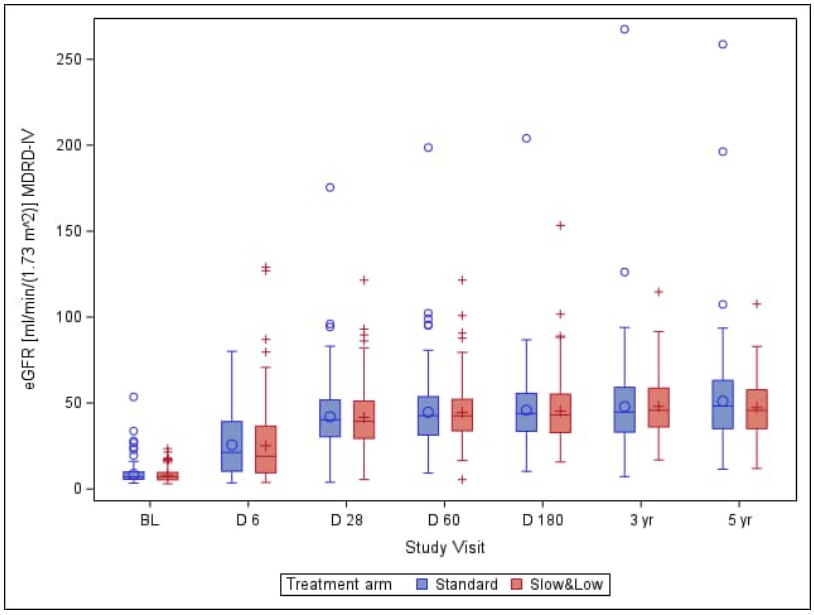

Figure **8** Course of eGFR according to MDRD-IV

Estimated GFR acc. to MDRD-IV formular shows a similar course in both groups. In a mixed model for square root of eGFR MDRD-IV values with patient as random effect, no statistically significant treatment effect was observed (F=0.01; p=0.913). Several imputation methods for missing values show similar results.

6.6.3 Course of eGFR according to CKD-EPI

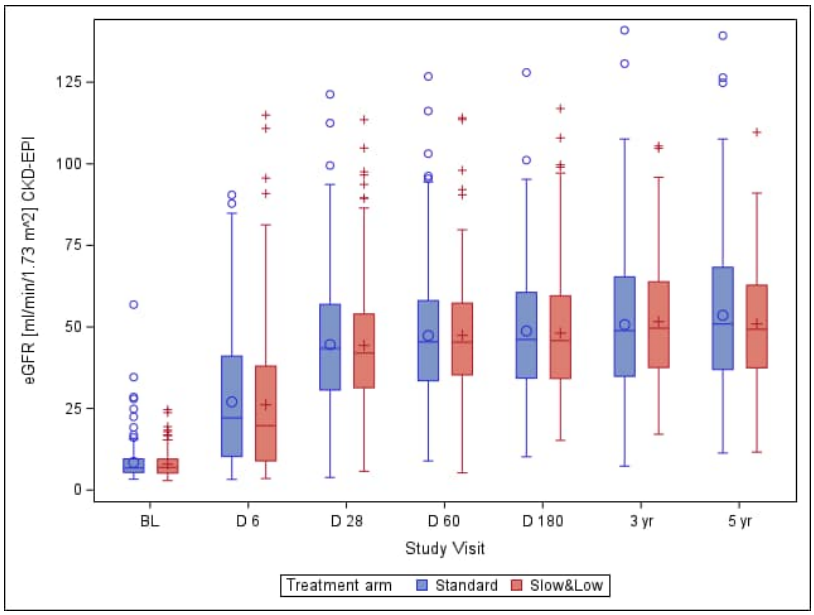

Figure **9** Course of eGFR according to CKD-EPI

Estimated GFR acc. to CKD-EPI formular shows a similar course in both groups. In a mixed model for square root of eGFR CKD-EPI values with patient as random effect, no statistically significant treatment effect was observed (F=0.00; p=0.955). Several imputation methods for missing values show similar results.

6.6.4 Course of eGFR according to Nankivell

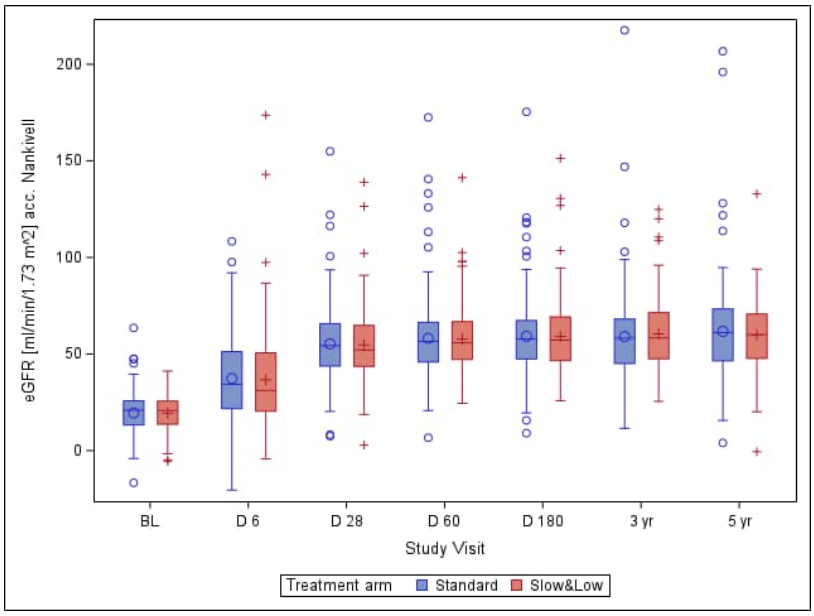

Figure **10** Course of eGFR according to Nankivell

Estimated GFR acc. to Nankivell formular shows a similar course in both groups. In a mixed model for square root of eGFR Nankivell values with patient as random effect, no statistically significant treatment effect was observed (F=0.05; p=0.832). Several imputation methods for missing values show similar results.

6.6.5 Delayed Graft Function

	Standard Care Arm	Slow & Low Arm	Treatment Effect (3) and 95% CI	p-value
	N = 202	N = 196		
Delayed graft function(1,2) (acc. to need for dialysis) [n (%)]	22 / 201 (10·9%)	21 / 194 (10·8%)	-0·1 [-6·3; 6·0]	1·000 (4)
Delayed graft function(1) (assessed by trial site) [n (%)]	42 / 201 (20·9%)	31 / 194 (16·0%)	-4·9 [-12·5;2·7]	0·243 (4)
(1) One patient in standard care arm and 2 patients in slow and low arm terminated study before day 7. (2) defined as need for dialysis after transplantation, i.e. at least one dialysis within 4 days after TX followed by at least one other dialysis until day 7. The need for dialysis must not be caused by graft rejection or graft loss. (3) Absolute risk difference (4) Fisher's exact test (two-sided)				

Table **7** Delayed graft function in ITT population

6.6.6 Rate of donor specific Anti-human leukocyte antigen (HLA) antibodies at 6 month and during follow up

	Standard Care Arm	Slow & Low Arm	Treatment Effect(1) and 95% CI	p-value (2)
	N = 202	N = 196		
Anti-HLA antibodies investigated within 6 months [n (%)]	155 (76·7%)	151 (77·0%)		
de novo, thereof [n (%)]	26 (16·8%)	15 (9·9%)	-6·8 [-14·4; 0·7]	0·094
not donor specific [n (%)]	21 (13·5%)	6 (4·0%)	-9·6 [-15·8; -3·4]	0·004
donor specific [n (%)]	5 (3·2%)	9 (6·0%)	2·7 [-2·0; 7·4]	0·285
Anti-HLA antibodies investigated during follow up period(3) [n (%)]	144 / 187 (77·0%)	152 / 179 (84·9%)		
any de novo Anti-HLA antibody detected [n (%)]	24 / 144 (16·7%)	25 / 152 (16·5%)	-0·2 [-8·7; 8·3]	1·000
any de novo donor specific Anti-HLA antibody detected [n (%)]	6 / 144 (4·2%)	8 / 152 (5·3%)	1·1 [-3·7; 5·9]	0·787
(1) Absolute risk difference (2) Fisher's exact test (two-sided) (3) restricted to patients in follow up (n=366)				

Table **8** Donor specific Anti-human leukocyte antigen (HLA) antibodies in ITT population

6.6.7 Changes in histology (IFTA, BKV-nephropathy, relapse of primary disease)

The number of patients with biopsy proven IFTA, BKV nephropathy, and relapse of underlying disease is given in the following table. No disadvantage was observed for the slow and low arm.

	Standard Care Arm	**Slow & Low Arm**	**Treatment Effect (1) and 95% CI**	**p-value (2)**
	N = 202	**N = 196**		
Interstitial fibrosis and tubular atrophy				
within first 6 months	30 (14·9%)	33 (16·8%)	1·9 [-5·2; 9·2]	0·681
during whole study	34 (16·8%)	35 (17·9%)	1·1 [-6·4; 8·5]	0·793
BKV nephropathy				
within first 6 months	3 (1·5%)	4 (2·0%)	0·5 [-2·0; 3·1]	0·720
during whole study	10 (5·0%)	5 (2·6%)	-2·4 [-6·1; 1·3]	0·293
Relapse of primary disease				
within first 6 months	1 (0·5%)	0 (0·0%)	-0·5 [-1·5; 0·5]	1·000
during whole study	2 (1·0%)	1 (0·5%)	-0·5 [-2·2; 1·2]	1·000

(1) Absolute risk difference
(2) Fisher's exact test (two-sided)

Table **9** Changes in histology

6.6.8 Dose modification of Advagraf®

	Standard Care Arm	Slow & Low Arm	p-value (1)
	N = 202	N = 196	
Advagraf® discontinued within 28 days after transplantation	12 (5.9%)	9 (4.6%)	
Any change of Advagraf® dose within 28 days after transplantation	201 (99.5%)	182 (92.9%)	
Number of changes of Advagraf® within 28 days after transplantation	6 [4 - 7]	3 [2 - 5]	<.001
Number of changes of Advagraf® dose between day 7 and 28 after transplantation, i.e. first week excluded	3 [2 - 5]	3 [2 - 4]	0.033
Data are presented as absolute and relative frequencies. (1) Mann-Whitney-U-test.			

Table **10** Dose modification of Advagraf®

As expected, more dose modification occurred in standard care arm.

6.7 SECONDARY ENDPOINTS OF SAFETY

6.7.1 Summary Adverse Events and Serious Adverse Events

Reporting of (serious) adverse events was restricted to first 6 months after renal transplantation. Afterwards, events of interest were reported as follow up complications, see chapter 6.7.5.

Almost all patients experienced at least one adverse event (standard care arm 200 (99·0%); slow and low arm 193 (98·5%)) during the reporting period. A brief summary of adverse event data is given in the next table.

	Standard Care Arm	**Slow & Low Arm**	**Treatment Effect(3) and 95% CI**	**Fisher's Exact p-value**
	N = 202	**N = 196**		
Patients with any adverse event [n (%)] during first 6 months after transplantation	200 (99·0%)	193 (98·5%)	-0·5 [-2·7;1·7]	0·681
Thereof, patients with any				
Adverse reaction(1)	103 (51·0%)	88 (44·9%)	-6·1 [-15·9; 3·7]	0·230
Serious adverse event	134 (66·3%)	136 (69·4%)	3·1 [-6·1; 12·2]	0·522
Serious adverse reaction(2)	37 (18·3%)	35 (17·9%)	-0·4 [-8·0; 7·1]	1·000

(1) Relationship to IMP assessed as possible, probable or certain by investigator at trial site·
(2) Relationship to IMP assessed as possible either by investigator at trial site or by person responsible for second assessment·
(3) Absolute risk difference·

Table **11** Adverse Events during first 6 months after transplantation

During the reporting period, 111 serious adverse reactions were reported without any imbalance between treatment groups (standard care 58 events, slow and low 53 events).

In total, 5 SUSAR in 3 patients were reported (standard care arm 3 events, slow and low arm 2 events). The events reported were:

Treatment arm	**SUSAR(s) by patient**
Standard care	delayed graft function
	wound-healing disturbance, ureter leakage
Slow and Low	Wound dehiscence, ureter leakage

6.7.2 Frequency of bacterial or viral infection

	Standard Care Arm	Slow & Low Arm	Treatment Effect (1) and 95% CI	Fisher's Exact p-value
	N = 202	N = 196		
Any infection within first 6 months	123 (60·9%)	113 (57·7%)	-3·2 [-12·9; 6·4]	0·541
Any infection during whole study	139 (68·8%)	128 (65·3%)	-3·5 [-12·7; 5·7]	0·522

(1) Absolute risk difference
(2) Fisher's exact test (two-sided)

6.7.3 Polyoma / BKV infection

	Standard Care Arm	Slow & Low Arm	Treatment Effect (1) and 95% CI	Fisher's Exact p-value
	N = 202	N = 196		
within first 6 months				
BKV infection indicated by a viral blood load of more than 1000 copies/µl	24 (11·9%)	17 (8·7%)	-3·2 [-9·2; 2·8]	0·325
BKV infection indicated by a viral blood load of more than 1000 copies/µl requiring treatment	2 (1·0%)	4 (2·0%)	1·0 [1·4; 3·5]	0·443
during whole study				
BKV infection indicated by a viral blood load of more than 1000 copies/µl	26 (12·9%)	17 (8·7%)	-4·2 [-10·3; 1·9]	0·198
BKV infection indicated by a viral blood load of more than 1000 copies/µl requiring treatment	4 (2·0%)	4 (2·0%)	0·06 [-2·7; 2·8]	1·000

(1) Absolute risk difference

6.7.4 Posttransplantation Diabetes mellitus

The analysis of posttransplantation diabetes mellitus (PTDM) was restricted to patients without diabetes mellitus of any type at the beginning of the clinical trial (n=334).

Within the first 6 months, incidence of PTDM was similar in both treatment arms, where 63/164 (38·4 %) Slow & Low arm recipients without pre-existing diabetes mellitus fulfilled at least one ADA criteria during study period and 64/167 (38·3 %) in the Standard Care arm.

At the end of the whole trial, a total of 137 events occurred (standard care arm 96 events and slow and low arm 98 events), most of them in the first year.

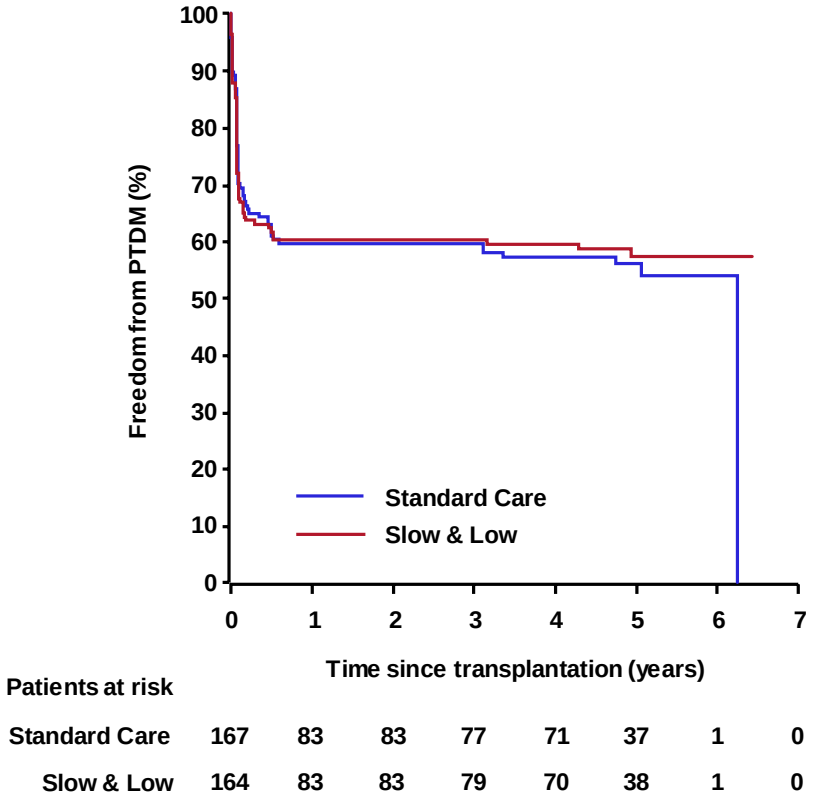

Figure **11** Kaplan Meier plot of PTDM in ITT population

Event rates of both arms are comparable (log rank test p = 0.817).

	Standard Care Arm	**Slow & Low Arm**
	N = 167	**N = 164**
PTDM rate (Kaplan Meier estimates)		
6 months after transplantation	37·7% [30·7%; 45·7%]	38·2% [31·2%; 46·2%]
3 years after transplantation	40·5% [33·3%; 48·5%]	39·6% [32·5%; 47·7%]
5 years after transplantation	43·9% [36·4%; 52·2%]	42·6% [35·1%;51·0%]

Table **12** Posttransplantation diabetes mellitus in ITT population

6.7.5 Complications during Follow Up

The analysis of complications reported during follow up period was restricted to patients who did not prematurely terminate clinical trial before follow up started (n = 366).

Frequencies of PTDM and infections during follow up are reported in chapter 0 to 0.

	Standard Care Arm	Slow & Low Arm	Treatment Effect(1) and 95% CI	Fisher's Exact p-value
	N = 187	N = 179		
Any complication during follow up, thereof	73 (39·0%)	61 (34·1%)	-4.9 [-14.8; 4.9]	0·331
Any infection	43 (23.0%)	36 (20.1%)	-2.9 [-11.3; 5.5]	0.527
Fracture	0 (0·0%)	0 (0·0%)	-	-
Malignancy, thereof	14 (7·5%)	18 (10·1%)	2.6 [-3.2; 8.4]	0·460
Skin cancer	6 (3·2%)	4 (2·2%)	-1.0 [-4.3; 2.4]	0·751
PTLD	1 (0·5%)	2 (1·1%)	0.6 [-1.3; 2.4]	0·616
Solid tumor	9 (4·8%)	11 (6·1%)	1.3 [-3.3; 6.0]	0·649
Not otherwise specified	0 (0.0%)	2 (1.1%)	-	-
Heart insufficiency	3 (1·6%)	3 (1·7%)	0.07 [-2.5; 2.7]	1·000
Myocardial infarction	0 (0·0%)	0 (0·0%)	-	-
Venous thrombosis(2)	3 (1·6%)	4 (2·2%)	0.6 [-2.2; 3.5]	0·719
Cerebrovascular disease	5 (2·7%)	1 (0·6%)	-2.1 [-4.7; 0.4]	0·216
Periphere vascular disease	2 (1·1%)	0 (0·0%)	-1.1 [-2.5; 0.4]	0·499
Hyperlipoproteinemia	0 (0·0%)	2 (1·1%)	1.1 [-0.4; 2.7]	0·239
Arterial hypertension	1 (0·5%)	0 (0·0%)	-0.5 [-1.6; 0.5]	1·000
Anemia	1 (0·5%)	0 (0·0%)	-0.5 [-1.6; 0.5]	1·000

(1) Absolute risk difference.
(2) deep vein thrombosis, pulmonary embolism.

7 CONCLUSION

Based on the ELITE Symphony study (Ekberg et al. 2007), immunosuppressive therapy with low-dose tacrolimus, mycophenolic acids and steroids after induction with an interleukin-2 receptor antibody has become the standard of care worldwide after kidney transplantation. Since that time, many studies exploring new immunsuppressive drug developments/concepts failed as comparators to this standard therapy. Nevertheless, especially during the early phase after transplantation, the perfect therapeutic window between safety/toxicity and efficacy of tacrolimus dosing/monitoring and handling has not been well-defined. Even within the Symphony study with relatively low tacrolimus levels, significant toxicity could still be observed. Many studies suggest that early calcineurin inhibitor toxicity or lack of efficacy affect DGF, kidney function, infections, PTDM or graft rejection/loss. These early effects indirectly influence hospital stay and health care costs but also long term outcome of renal transplant recipients. Especially fluctuating tacrolimus trough levels frequently occur in the early phase after transplantation due to individual variability of tacrolimus pharmacokinetics, bowel movement, and/or corticosteroid-mediated Cyp450 enzyme induction. While drug monitoring is highly recommended for this initial phase, mostly daily trough level monitoring with frequent tacrolimus dose changes as done in many transplant centers add to this variability. A search in PubMed and Google Scholar Search Engines through January 14, 2025, using the keywords "renal transplantation", "immunosuppression", "tacrolimus", and "fixed dose" did not reveal any prospective studies that further examined fixed doses of tacrolimus in the immediate early phase after renal transplantation. A single manuscript by Jiang-Tao Tang in 2018 examined whether a low fixed starting tacrolimus dose could lead to better achievement of tacrolimus target concentrations as well as effective immunosuppressive treatment in Chinese kidney transplant recipients. This was a non-randomized study and a post-hoc comparison of different fixed doses between 2 and 3 mg of tacrolimus per day. Studies exploring an easy to handle, low tacrolimus, bottom up principle using a fixed dose of prolonged release tacrolimus administered for the first six days after renal transplantation without trough level determinations are not available.

At 6-months after kidney transplantation the Slow & Low, fixed dose tacrolimus dosing arm showed non-inferiority compared to the standard immunosuppressive therapy regarding the combined primary endpoint of BPAR, graft loss, and death. This overall result was applicable to a wide range of transplant recipients, robust and independent of the inclusion or exclusion of borderline or protocol rejections in the primary endpoint. The low fixed dose concept was extremely easy to handle and safe. This study also demonstrated that early reduced tacrolimus exposure leads to an earlier apparence of BPARs, a slight severity shift of borderline towards T-cell mediated BANFF Ia rejections without changing incidences of delayed graft function, kidney function, post transplantation diabetes mellitus, infections or development of donor specific antibodies.

In the follow-up period extending to 3 and 5 years after kidney transplantation, the results from both the standard treatment arm and the Slow & Low, fixed-dose tacrolimus dosing arm remained comparable with respect to the primary endpoint, which included biopsy-proven acute rejection (BPAR), graft loss, and death. Although T-cell-mediated rejections occurred earlier in the Slow & Low arm, this timing difference did not significantly affect long-term outcomes such as graft loss or patient survival. Both graft survival and patient survival rates were similar in both treatment arms, further supporting the conclusion that the Slow & Low, fixed-dose tacrolimus regimen is not inferior to standard immunosuppressive therapy, even over extended follow-up periods of 3 to 5 years.

These findings suggest that the fixed-, low-dose regimen remains a safe and effective bottom up alternative for long-term immunosuppression following kidney transplantation. No increased risk of adverse outcomes, such as the development of HLA antibodies, infections, or post-transplant diabetes mellitus, was observed in the Slow & Low group when compared to the standard regimen. This reinforces the potential of the easy to handle Slow & Low dosing approach to provide a viable option for maintaining long-term graft function and patient survival without compromising safety.

8 PUBLICATIONS

Stumpf, Julian; Budde, Klemens; Witzke, Oliver; Sommerer, Claudia; Vogel, Thomas; Schenker, Peter et al. (2024): Fixed low dose versus concentration-controlled initial tacrolimus dosing with reduced target levels in the course after kidney transplantation: results from a prospective randomized controlled non-inferiority trial (Slow & Low study). In: *EClinicalMedicine* 67, S. 102381. DOI: 10.1016/j.eclinm.2023.102381.

9 SIGNATURES

The signing persons approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable legal regulations.

Sponsor

Prof. Dr. Christian Hugo		
Name in block letters	Place, Date	Signature

Biostatistics

Evelyn Trips		
Name in block letters	Place, Date	Signature

10 LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	adverse event
AMG	Arzneimittelgesetz
AR	adverse reaction
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BKV	BK virus = human polyomavirus 1
BPAR	biopsy proven acute rejection
BW	body weight
CI	confidence interval
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DGF	delayed graft function
EBV	Epstein Barr virus
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
ESP	European Senior Program
FPFV	First patient first visit
FU	follow up
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
I/E	inclusion/exclusion
IFTA	interstitial fibrosis and tubular atrophy
IMP	investigational medical product
IQR	inter quartile range
ITT	intention to treat
KKS	Koordinierungszentrum für Klinische Studien
LPLV	Last patient last visit
MMF	mycophenolate mofetil
NA	not applicable
ND	not done
NODAT	new onset diabetes mellitus after transplantation
PCR	polymerase chain reaction
PPS	per protocol set

PRA	panel-reactive antibodies
PTDM	posttransplantation diabetes mellitus
PTLD	Post-transplant lymphoproliferative disorders
SAE	serious adverse event
SAR	serious adverse reaction
SAS	safety analysis set
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
UAR	unexpected adverse reaction

11 REFERENCES

Brand, J. P. L. (1999): Development, Implementation, and Evaluation of Multiple Imputation Strategies for the Statistical Analysis of Incomplete Data Sets.

Ekberg, Henrik; Tedesco-Silva, Helio; Demirbas, Alper; Vítko, Stefan; Nashan, Björn; Gürkan, Alp et al. (2007): Reduced exposure to calcineurin inhibitors in renal transplantation. In: *The New England journal of medicine* 357 (25), S. 2562–2575. DOI: 10.1056/NEJMoa067411.

Levey, Andrew S.; Coresh, Josef; Greene, Tom; Stevens, Lesley A.; Zhang, Yaping Lucy; Hendriksen, Stephen et al. (2006): Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. In: *Annals of internal medicine* 145 (4), S. 247–254.

Levey, Andrew S.; Stevens, Lesley A.; Schmid, Christopher H.; Zhang, Yaping Lucy; Castro, Alejandro F. 3rd; Feldman, Harold I. et al. (2009): A new equation to estimate glomerular filtration rate. In: *Annals of internal medicine* 150 (9), S. 604–612.

Nankivell, B. J.; Gruenewald, S. M.; Allen, R. D.; Chapman, J. R. (1995): Predicting glomerular filtration rate after kidney transplantation. In: *Transplantation* 59 (12), S. 1683–1689.

Stumpf, Julian; Budde, Klemens; Witzke, Oliver; Sommerer, Claudia; Vogel, Thomas; Schenker, Peter et al. (2024): Fixed low dose versus concentration-controlled initial tacrolimus dosing with reduced target levels in the course after kidney transplantation: results from a prospective randomized controlled non-inferiority trial (Slow & Low study). In: *EClinicalMedicine* 67, S. 102381. DOI: 10.1016/j.eclinm.2023.102381.

van Buuren, Stef (2007): Multiple imputation of discrete and continuous data by fully conditional specification. In: *Statistical methods in medical research* 16 (3), S. 219–242. DOI: 10.1177/0962280206074463.