Clinical Study Report

Study:

Anti-donor alloreactivity-guided CNI minimization versus unguided standard triple therapy in living-donor kidney transplantation

(ICANMINI)

Study Code:	ICANMINI
Eurdract-No.	2015-002465-28
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Klinikum der Universität München
Marchioninistraße 15
81377 München
GERMANY

1 TITLE PAGE

Study Title	Anti-donor alloreactivity-guided CNI minimization versus unguided standard triple therapy in living-donor kidney transplantation (ICANMINI)
Name of Test medication	Advagraf® / Envarsus® (prolonged release tacrolimus)
Indication studied	De novo living donor renal transplantation
Design	Randomized, controlled, open label, parallel group, efficacy, and safety study
Name of Sponsor	Klinikum der Universität München
Protocol	Amendment 01, dated 30-Jan-2019
Phase of development	IV
Studied period	23/05/2016 – 05/02/2021
Sponsor delegated person and principal investigator	Prof. Dr. med. Markus Guba
Name of sponsor signatory	Prof. Dr. med. Markus Guba
Date of report	31-MAY-2022

This study was performed according to the principles of the current edition of the declaration of Helsinki, according to the German Drug Law (AMG), and according to Good Clinical Practice (GCP), including the archiving of essential documents.

2 SYNOPSIS

PROTOCOL ID:
ICANMINI

EudraCT-No.:
2015-002465-28

Study Title:
Anti-donor alloreactivity-guided CNI minimization versus unguided standard triple therapy in living-donor kidney transplantation

Study Product:
Prolonged release tacrolimus (Advagraf® or Envarsus®)

SPONSOR:
Klinikum der Universität München
Marchioninistraße 15,
81377 München, Germany

STUDY SITE(S) AND INVESTIGATOR(S):
The study was conducted at a single site.

Principal Investigator:
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81377 München, Germany

METHODOLOGY:

Study Design:
Randomized, controlled, open label, parallel group, efficacy, and safety study, comparing a standard CNI minimization to an accelerated CNI minimization under alloimmune response guidance in adult de novo living donor renal transplant recipients.

Development Phase:
Phase IV

Study Objectives:
To evaluate the effect of an anti-donor alloreactivity guided CNI minimization on the evolution of renal function.

Further objectives are to evaluate the effects on BPAR, graft loss or death and the composite efficacy failure rate, to compare the safety and to explore influences of immunological parameters.

Study Population:
100 adult living-donor kidney transplant recipients (n= 40 unguided minimization group, n=60 guided minimization group) were planned.

Main criteria for inclusion:

Male or female subjects ≥ 18 years of age. Subjects must be recipients of a primary renal transplant from a living unrelated, living related non-human leukocyte antigen identical donor.

Immunized patients with a current PRA > 5% and recipients of an ABO incompatible allograft or a CDC crossmatch positive transplant were excluded.

Study Plan:
After checking for inclusion/exclusion criteria and prior to transplantation patients were randomized in a 1:1.5 ratio to either unguided control (UC) or guided accelerated minimization (IM) therapy. Prolonged release tacrolimus (PR-TAC) is started 24h prior to transplantation at a dose of 0.2 mg/kg/d Advagraf® or 0.17 mg/kg/d Envarsus® and thereafter administered according to the randomized treatment plan. During 4 weeks after transplantation all subjects receive a standard dose immunosuppression with prolonged release tacrolimus + EC mycophenolic acid (Myfortic 720 mg bid) + Prednisolone (tapered to 5 mg/d at week 4). Tacrolimus target trough levels for the first 4 weeks were 8-12ng/ml. Assessments were planned 1, 2, 3 , and 4 weeks after transplantation and thereafter at week 12, at month 6 and finally at 12 months after transplantation.

Blood samples for the immunological assessments were taken at baseline and at week 4, week 12, month 6, and month 12 after transplantation.

After 4 weeks unguided controls continued PR-TAC dosing with a target trough level of 8-12 ng/ml and patients in the immune response guided treatment group received reduced PT-TAC dosing with a target trough level of 6-8 ng/ml if they were negative for INFγ and donor specific HLA antibodies (DSA) and had no BPAR.

12 weeks after transplantation PR-TAC dose was reduced in the control group to 6-8 ng/ml target trough level. In the immune guided group, the dose was further reduced with a target trough level of 4-6 ng/ml if negative for INFγ, DSA, and BPAR.

At 6 months after transplantation patients negative for INFγ and DSA and BPAR stayed on their dosing target of 4-6 ng/ml. Patients in the control group stayed on their target of 6-8 ng/ml.

During the whole treatment period patients in the guided minimization group were switched to and stayed on the same dosing scheme as in the control group at any time when they were either positive for INFγ or DSA or are diagnosed with BPAR. Mycophenolic acid (720 mg b.i.d.) and steroids (max. 5mg/d) were continued unchanged in both treatment arms.

Study Product and Treatment:
Investigational:

Anti-donor alloreactivity-guided CNI minimization with prolonged-release tacrolimus, EC mycophenolic acid (720 mg b.i.d.) and steroids.

Tacrolimus target trough levels 8-12 ng/ml 0-w4, 6-8 ng/ml w5-w12; 4-6 ng/ml w13-m12

Reference:

Unguided standard triple therapy with prolonged-release tacrolimus, EC mycophenolic acid (720 mg b.i.d.) and steroids.

Tacrolimus target trough levels 8-12 ng/ml 0-w4, 8-12 ng/ml w5-w12; 6-8 ng/ml w13-m12

Main Criteria for Evaluation:

Efficacy:

Primary endpoint:

- eGFR at 12 months after transplantation calculated by the 4-variable MDRD formula

Secondary endpoints:

- Effect on further renal function parameters (S-Creatinine, Cockroft-Gault, Nankivell, CKD-EPI)
- Incidence of graft loss
- Incidence of death
- Incidence oft BPAR
- Effect on a composite efficacy failure rate of treated biopsy proven acute rejection (tBPAR), graft loss or death or eGFR < 50 ml/min/1.72m^2 calculated by the MDRD-4 formula

Safety:

- The incidence of adverse events, serious adverse events and adverse events leading to study regimen discontinuation

Statistical Analysis:

Sample size estimation was based on the primary endpoint. Assuming a difference in eGFR 12 months after transplantation of 10 ml/min/1.73m^2 and a standard deviation of 16 ml/min/1.73m^2 a total of 90 patients are required for a 1:1.5 ratio in the treatment groups. With regard to 10% possible dropouts 100 patients should be included.

The primary analysis had to be performed in the intention-to treat population of unguided patients compared to immune monitored patients. The primary parameter, defined as eGFR at 12 months after transplantation was planned to be tested by means of the Wilcoxon rank sum test.

All other relevant efficacy and safety parameters were evaluated in an explorative, descriptive manner using appropriate statistical methods. For these analyses p-values (two-sided) < 0.05 were considered statistically significant but are provided for descriptive reasons only.

Study Period:

First Patient First Visit: 23-May-2016

Last Patient Last Visit: 05-Feb-2021

RESULTS:

Study Population:

A total of 35 patients were enrolled and randomly assigned to the immune monitoring group (N=21) and the unguided control group (N=14). All patients received study treatment and were analysed according to the intent to treat principle. The recipients were 22.9% female and 97.1% Caucasian with a median age of 34 years at inclusion (range: 19-63 years). Donors were 54.3% female, with a median age of 56 years (range: 43-70). In demographic and baseline data no relevant differences were found between the treatment groups.

Tacrolimus Minimization and Tacrolimus Trough Levels:

During the study only 3 patients (all in the IM group) had neither positive INFγ or DSA or developed no BPAR and could receive the lower PR-TAC dose. The analysis of TAC trough levels during the study showed a similar profile in both arms, with a maximum at 12 weeks after transplantation with subsequent decline. Only at the 12 months visit a significantly lower TAC trough level was observed

in the immune guided group, compared to the unguided control.

Primary Endpoint:
The primary endpoint was defined as eGFR calculated according to the 4 variable MDRD formula at 12 months after transplantation. The result shows a numerically lower eGFR in the immune monitored group but no statistically significant difference. The result does not support the study hypothesis of a possible gain in renal function with immune guided minimization of tacrolimus. Sensitivity analyses and a per protocol analysis gave comparable results.

eGFR (MDRD-4) [ml/min/1.73 m^2]	**IM (immune monitored)**	**UC (unguided control)**
N	21	14
Mean ± SD	52.6±16.9	60.7±12.7
Median (Q1-Q3)	53.9 (43.1-60.4)	58.5 (50.2-66.0)
P=0.1524 (Wilcoxon rank sum test)		

Secondary Efficacy Endpoints:
Serum creatinine and creatinine clearance by the Cockroft-Gault, as well as eGFR by Nankivell or CKD-EPI formula do not show any significant differences at 12 months after transplantation and support the result found for the primary endpoint. During the 12-month study period no deaths and no graft failures were recorded. Biopsy proven acute rejections have all been treated and account for 7 (22.3%) in the immune monitored group and 5 (35.7%) in the unguided control. Banff 4 rejections were 3 (14.3%) and 4 (28.6%) in the IM and the UC group respectively. A composite efficacy failure was defined as a subject having a treated biopsy proven acute rejection (tBPAR), graft loss or death or eGFR < 50 ml/min/1.72m^2. The composite efficacy failure rate was evaluated to 47.6% (N=10) in the immune monitored group and to 50% (N=7) in the unguided control.

	IM (immune monitored) (N=21)	**UC (unguided control) (N=14)**	
Parameter	**Mean±SD or N(%)**	**Mean±SD or N(%)**	**P**
Creatinine (S-Cr)[mg/dl]	1.73±0.93	1.39±0.25	0.3703 [1)]
Crea-Cl.(Cockroft Gault) [ml/min/1.73 m^2]	60.15±18.45	68.73±15.25	0.1835 [1)]
eGFR (Nankivell) [ml/min/1.73 m^2]	60.64±16.01	66.59±12.04	0.2888 [1)]
eGFR (CKD-EPI) [ml/min/1.73m^2]	54.88±18.53	63.28±15.41	0.2453 [1)]
tBPAR	7 (33.3)	5 (35.7)	1.0000 [2)]
Banff 4	3 (14.3)	4 (28.6)	0.4007 [2)]
Composite efficacy failure	10 (47.6)	7 (50.0)	1.0000 [2)]
Death	None	None	
Graft failure	None	None	
1) Wilcoxon rank sum test 2) Fishers Exact Test			

Safety Results:

The overall safety findings showed a total of 211 adverse events (AE) (146 in the immune guided group and 65 in the unguided control). The majority of the events were mild to moderate with no differences between treatment groups. Only 49 AE (23.2%) were considered to have a causal relationship to study medication.

All patients had at least one AE. The most common AE System Organ Classes (SOCs) were Investigations (76%) > Infections and infestations (57%) > Gastrointestinal disorders (52%) > Blood and lymphatic system disorders (38%) > Immune system disorders (38%) in the IM group and Investigations (57%) > Infections and infestations (50%) > Nervous system disorders (50%) > Immune system disorders (36%) > Injury, poisoning and procedural complications (36%) in the UC group. On the preferred term level, the highest incidence was kidney transplant rejection (34%), tremor (31%) and diarrhoea (26%) with no differences between treatment groups. 27 patients (77%) had at least one treatment related AE with the highest incidence in the SOCs infections and infestations (37%), nervous system disorders (29%), and investigations (23%).

In each group one patient was withdrawn from the study product due to an adverse event.

A total of 21 SAE was reported (12 in the IM and 9 in the UC group), only 7 were rated as treatment related. The incidence of patients reporting a serious adverse event was 33% in the IM and 43% in the UC group.

The overall safety profile of the study medications was as expected from previous experience in renal transplant patients. No differences were detected between the treatment groups.

No safety concerns were identified in the laboratory data or vital signs reported during the study.

CONCLUSIONS:

The data available after discontinuation of the study do not show any significant differences between the treatment arms. The primary analysis 12 months after transplantation could not prove a difference in renal function measured as eGFR by the 4 variable MDRD formula between an immune guided minimization compared to the unguided control. The results of the primary endpoint are consistent with secondary endpoints and a per protocol analysis. No evidence was found that the proposed alloimmune guided tacrolimus minimization will lead to a better long term renal function than the standard unguided control.

Safety analyses showed no notable differences between the treatment groups. The safety data are consistent with the known safety profile of immunosuppression with tacrolimus, mycophenolic acid, and prednisolone.

Version / Date of CSR:

1.0 **/** 31-MAY-2022

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialist term	Explanation
AB0	ABO blood group system based on anti-A and anti-B antibodies
AD	Available Data
ADV	Advagraf®
AE	Adverse Event
ALT (SGPT)	Alanine Transaminase (Serum Glutamate Pyruvic Transaminase)
AMG	Arzneimittelgesetz (German drug law)
AST (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Chemical Classification System
B cell	Lymphocyte of “bursal” origin; progenitor of antibody-producing cells
b.i.d.	Twice (two times) a day (lat. “bis in die”)
Banff	Diagnostic categories for renal allograft biopsies; schema initially developed in Banff, Canady 1991
BPAR	Biopsy Proven Acute Rejection
CDC crossmatch	Complement-dependent cytotoxicity crossmatching test for detecting donor-specific anti-human leukocyte antigen (HLA) antibodies
CI	Confidence interval
CNI	Calcineurin Inhibitor
CPK	Creatine Phosphokinase
CrCl	Creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DGF	Delayed Graft Function
DNA	Deoxyribonucleic Acid
DSA	Donor Specific Antibody
EC	Enteric Coated
eGFR	Estimated Glomerular Filtration Rate
Elispot	Enzyme-Linked Immunosorbent Spot Assay
ENV	Envarsus®
EU	European Union
FCBP	Female of Child Bearing Potential
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transferase (Transpeptidase)
GKV	Gesetzliche Krankenversicherung (statutory health insurance)
H0	Null hypothesis
HA	Alternate hypothesis

Abbreviation or specialist term	Explanation
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen; the human major histocompatibility complex of antigens
ICD-10	10th Revision of the International Statistical Classification of Diseases and Related Health Problems
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Immune monitoring (group)
INFg	Interferon gamma
INR	International Normalized Ratio
ITT	Intent To Treat
IUD	Intrauterine Device
LCLM	Lower Confidence Limit of the Mean
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lowe Limit of Normal
LPLV	Last Patient Last Visit
LUMINEX	Luminex Corporation, developing biological testing technologies
MAR	Missing at Random
MAX	Maximum
MDRD-4	Modification in Diet in Renal Disease; 4 variable eGFR calculation
MEAN	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
MEDIAN	Median value (50% percentile)
MFI	Mean Fluorescence Intensity
MIN	Minimum
MNAR	Missing not at Random
MPA	Mycophenolic Acid
MYF	Myfortic (enteric-coated mycophenolic acid)
N	Number of valid observations
NMISS	Number of missing observations
PBMC	Peripheral Blood Mononuclear Cell
PctN	Percent (%)
PDN	Prednisolone
PP	Per Protocol
PRA	Panel Reactive Antibodies
PRO	Prograf®
PR-Tac	Prolonged Release Tacrolimus
PT	Preferred term according to the MedDRA system

Abbreviation or specialist term	Explanation
PTT	Partial Thromboplastin Time
Q1	First quantile (25% perentile)
Q25	25% percentile
Q3	Third quantile (75% perentile)
Q50	Median
Q75	75% percentile
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical analysis plan
SDP	Sponsor Delegated Person
SmPC	Summary of Product Characteristics (Fachinformation)
SOC	System Organ Class according to the MedDRA system
SOP	Standard Operating Procedure
ß-HCG	β-subunit hCG (human chorionic gonadotropin); pregnancy test
STD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tac	Tacrolimus
T cell	Cell of thymic origin, involved in cellular immunity
TB	Tuberculosis
tBPAR	Treated Biopsy Proven Acute Rejection
Tx	Transplantation
UC	Unguided control (group)
UCLM	Upper Confidence Limit of the Mean
ULN	Upper Limit of Normal
WBC	White Blood Cell Count (Leucocytes)
WHO	World Health Organization

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

Prior to study start the study protocol and a sample of the informed consent form were approved by an independent Ethics Committee. The approval was gained by the EC responsible for the coordinating principal investigator, which was:

Ethikkommission der Med. Fakultät der LMU München
Pettenkoferstr. 8a
80336 München

The responsible ethics committee also received all the substantial amendments.

5.2 Ethical Conduct of the study

Prior to study start investigators attested by signature that this study had to be performed according to the principles of the current edition of the Declaration of Helsinki, according to German drug law (AMG), and according to Good Clinical Practice (GCP). This is known to both the investigators and to the sponsor representatives responsible for the conduct of this clinical trial.

The investigator could discontinue the treatment at any time if he/she felt that this was in the interest of the patient. Patients were free to discontinue the study at any time without explanations or other inconveniences.

Personal data of both, investigators, and patients, were stored and processed. Organizational procedures were implemented to protect these data by preventing their disclosure to unauthorized third parties. The procedures were in accordance with the REGULATION (EU) 2016/679 (General Data Protection Regulation) and the German law of processing personal data (Datenschutzgesetz) and the corresponding rules of the federal states.

5.3 Patient information and consent

Before a patient could be enrolled into the study investigators were obliged to obtain written informed consent from each patient after an oral and written explanation about the aim and the risks of the study and the nature of the investigational drug. The given information pointed out the patient's right to discontinue the study at any time and without any disadvantages. Written informed consent was requested from donors accordingly.

All patients were insured according to legal demands.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Administrative structure

The study was conducted mono-centric at the Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Klinikum der Universität München, Campus Großhadern with the sponsor Klinikum der Universität München Represended by: Prof. Dr. med. Karl-Walter Jauch (Ärztlicher Direktor).

Sponsor delegated person and principal investigator was Prof. Dr. med. Markus Guba. Data Management was performed by Algora Gesellschaft für Medizinstatistik und Vertriebssysteme mbH. A central laboratory were involved for analysis of blood samples for immunological parameters: Labor für Immungenetik und Molekulare Diagnostik, Abteilung für Transfusionsmedizin, Zelltherapeutika und Hämostaseologie, Klinikum der Universität München.

Datamanagement, monitoring and statistical analysis was performed by Algora Gesellschaft für Medizinstatistik und Vertriebssysteme mbH.

Serios adverse events were reported to the pharmaceutical companies Astellas Pharma GmbH and Chiesi GmbH for their respective products.

Role in Study	**Name**	**Contact Information**
Sponsor	Klinikum der Universität München Represended by: Prof. Dr. med. Karl-Walter Jauch (Ärztlicher Direktor)	Marchioninistraße 15, 81377 München, Germany Phone +49 (0) 89 / 4400-0 Fax +49 (89) 4400-72102 E-Mail: aed@med.uni-muenchen.de
Sponsor Delegated Person (SDP)	Prof. Dr. med. Markus Guba Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Klinikum der Universität München, Campus Großhadern,	Marchioninistraße 15, 81377 München, Germany Phone +49 (0) 89 / 4400-72790 Fax +49 (0)89 / 4400-778893 E-Mail: Markus.Guba@med.uni-muenchen.de
Principal Investigator	Prof. Dr. med. Markus Guba Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Klinikum der Universität München, Campus Großhadern,	Marchioninistraße 15, 81377 München, Germany Phone +49 (0) 89 / 4400-72790 Fax +49 (0)89 / 4400-778893 E-Mail: Markus.Guba@med.uni-muenchen.de

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Drug Safety Contact	Astellas Pharma GmbH Chiesi GmbH	Georg-Brauchle-Ring 64-66 80992 München, Gemany Fax: 089-4544-1148 E-Mail: **de-pharmacovigilance@astellas.com** Gasstraße 6 22761 Hamburg Telefax: 040 897 24 270 E-Mail: DE-AMS@chiesi.com

6.2 Investigators

This is a study conducted at a single site.

Site No	Name and address
01	Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Klinikum der Universität München, Campus Großhadern, Marchioninistraße 15, 81377 München, Germany

7 INTRODUCTION

7.1 Background

The introduction of calcineurin inhibitors has significantly improved short-term renal graft survival by lowering acute rejection rates in kidney transplantation. Nonetheless, long-term transplant survival is still not satisfactory, with calcineurin inhibitor-induced chronic nephrotoxicity being one of the main causes of progressive nephron loss and declining renal transplant function. Hence, different immunosuppressant regimens have been proposed to avoid or ameliorate calcineurin inhibitor-induced nephrotoxicity [1]. CNI minimization and withdrawal strategies have yielded inconsistent results mainly due to latent under-immunosuppression in individual patients [2-4].

So far, the decision-making regarding type and amount of immunosuppression is essentially based on the clinician's perception of the initial immunological risk profile of a patient. Later on, maintenance therapy relies on measuring trough levels to keep immunosuppressive agents in an effective range. A precise and prospective immune monitoring to assess the anti-donor allo-immune status of renal transplant recipients at different time points to guide therapy is not yet established [5].

The occurrence of donor specific antibodies was associated with a persistence of allo-specific stimulation, which may also result in poor graft outcomes. It is assumed, that humoral allo-sensitization is a consequence of an ongoing immune response, which also involves alloreactive T-effector and memory cells [6-7]. Compared to naive T-cells, alloreactive effector/memory cells are long lived, have rapid recall effector function with reduced activation requirements, may also be influenced by heterologous activation and are generally less susceptible to immunosuppression. Thus, measuring highly alloreactive circulating memory/effector T-cells with donor-antigen specificity may help to tailor immunosuppression in an individual patient. Indeed, clinically detection of this cell population, using interferon-gamma enzyme-linked immunosorbent spot assays (Elispot) has been shown to discriminate patients at increased risk for T-cell mediated rejection and worse graft function evolution, even in absence of humoral allosensitization [8].

7.2 Rationale

This study prospectively assesses the value of an alloimmune response-guided accelerated CNI minimization as compared to a standard („blind") CNI minimization without the guidance of donor specific T-cell reactivity and donor specific humoral allosensitization.

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the effect of an anti-donor alloreactivity guided CNI minimization on renal function (eGFR calculated by the MDRD-4 formula) 12 months after transplantation.

8.2 Secondary Objectives

To evaluate the effect of an anti-donor alloreactivity guided CNI minimization compared to non-guided CNI minimization with respect to

- The incidence of graft loss at 12 months
- The incidence of death at 12 months
- The incidence of BPAR by severity and time to event
- The effect on common renal function parameters at 12 months and their change from baseline
- Composite efficacy failure rates based on incidence of BPAR, graft loss, death, and renal function.
- The incidence of adverse events, serious adverse events and adverse events leading to study regimen discontinuation.

8.3 Further Study Objectives

To explore:

- The incidence of donor reactive antibodies at 12 months (DSA)
- The incidence of cellular donor reactivity at 12 months (INFγ)
- The incidence of immune adaptation defined as donor to third party reactivity at 12 months
- The incidence of circulating donor derived DNA

Donor specific DNA:

The aim of this exploratory substudy is to quantify peripheral donor chimerism and to analyse its association with graft and recipient outcome.

Donor specific polymorphism are used to identify and detect donor derived DNA in peripheral blood of the recipient by means of AlleleSEQR Chimerism Assay (Celera/Abbott). The assay is highly sensitive and specific. The presence and levels as well as the course of donor specific DNA after transplantation should be analysed and correlated to the clinical outcome.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

This is a phase IV, randomized, controlled, open label, parallel group, efficacy, and safety study, comparing a standard CNI minimization to an accelerated CNI minimization under alloimmune response guidance in adult de novo living donor renal transplant recipients. Consented subjects meeting eligibility criteria will be randomized (1:1.5 between the unguided standard and the guided minimization group) into the 12-month treatment period.

9.1.1 Screening Phase and Baseline

Screening will be based on routine examinations including a period of up to 6 months prior to transplantation.

Study specific screening procedures will be performed within 24 hours prior to transplantation. Subjects willing to participate in the study have to sign a written informed consent prior to any study specific procedure, after being informed about the possible risks and possible benefits. Study specific procedures include vital signs, physical examination, and laboratory assessments prior to transplantation, as well as analysis of blood samples for DSA, INFγ, and donor specific DNA.

Assays to evaluate the immunological state (DSA, INFγ) at baseline have to be performed. Samples must be taken prior of the first dose of PR-Tac (Advagraf® or Envarsus®). Results remain blinded to the investigators.

Concurrent participation of donors is required, who also have to give their written informed consent prior to study specific procedures (blood sampling).

9.1.2 Randomization and Run-in Phase

The run-in phase begins with the start of immunosuppressive therapy. Prolonged-release tacrolimus is introduced 24h prior transplantation at a dose of 0.2 mg/kg/d with Advagraf® or 0.17 mg/kg/d Envarsus®.The initially chosen formulation should not be changed later during the study period.

Prior to transplantation and after checking all inclusion/exclusion criteria patients will be randomized 1:1.5 between the unguided standard and the guided minimization group.

During 4 weeks after transplantation all subjects will receive a standard dose CNI-based immunosuppression with prolonged-release tacrolimus (Advagraf® or Envarsus®) + EC mycophenolic acid (Myfortic, 720 mg bid as tolerated) + prednisolone (steroid according to centre practice). Steroids are tapered to 5 mg/d prednisolone at 4 weeks after transplantation following centre standards. Tacrolimus trough levels for the first 4 weeks are 8-12 ng/ml. Assessments are planned 1, 2, 3, and 4 weeks after transplantation as outlined in the Schedule of Assessments (Table 1).

9.1.3 Randomized Treatment Phase

After 4 weeks post transplantation assays to evaluate DSA and INFγ will be performed in all patients but results will be communicated to the investigator only for patients in the guided minimization group.

After 4 weeks of common run-in phase treatment will be applied according to the randomized treatment arm (**Fehler! Verweisquelle konnte nicht gefunden werden.**):

Patients in the unguided group will continue PR-Tac dosing with a target trough level of 8-12 ng/ml.

In the alloimmune response guided treatment group immunosuppressive treatment will be continued dependent on INFγ and DSA and BPAR after 4 weeks (**Figure 2**). Patients positive for any INFγ, DSA, or BPAR will retain their initial dose regimen as in the unguided group, whereas patients negative for INFγ and DSA and with no BPAR receive reduced PR-Tac dosing with a target trough level of 6-8 ng/ml. It is to mention, that the interval between sampling for immunological analysis and the therapeutic consequences (reduced PR-Tac dosing or not) may be up to 2 weeks.

In both treatment groups Mycophenolic acid (720 mg b.i.d.) and steroids (5 mg/d prednisolone or equivalent according to centre practice) are dosed identical.

12 weeks after transplantation tacrolimus dose will be reduced in the control group to 6-8 ng/ml target trough level. In the guided minimization group the reduction step is dependent on actual INFγ and DSA and BPAR results.

Patients negative for actual INFγ and DSA and BPAR will switch to a further reduced dose with a target trough level of 4-6 ng/ml, whereas patients positive for INFγ or DSA or BPAR will stay on their dose targeting to a trough level of 6-8 ng/ml. Assays to evaluate DSA and INFγ will be performed in all patients at the 12 weeks visit but results will be communicated to the investigator only for patients in the guided minimization group.

Mycophenolic acid (720 mg b.i.d.) and Steroids (maximal 5 mg/d prednisolone) will be applied identical in both treatment arms.

At 6 months after transplantation assays to evaluate DSA and INFγ will be performed again. No action will be taken on patients in the control group and DSA/ INFγ results remain blinded.

In the guided minimization group further treatment depends on INFγ and DSA and BPAR results. Patients positive for INFγ or DSA or BPAR will switch to an elevated dose targeting to a trough level of 6-8 ng/ml (next higher level). Patients negative for INFγ and DSA and BPAR will stay on their dosing targeting 4-6 ng/ml.

Mycophenolic acid (720 mg b.i.d.) and Steroids (maximal 5 mg/d prednisolone or equivalent) will be continued unchanged in both treatment arms.

During the whole treatment period patients in the guided minimization group are switched to and stay on the same dosing scheme as in the control group at any time when they are either positive for INFγ or DSA or are diagnosed with BPAR.

Trough levels should be kept in the upper target range in the control arm and in the lower target range in the guided minimization arm.

The study will be completed with an assessment 12 months after transplantation or at the time of premature end of study.

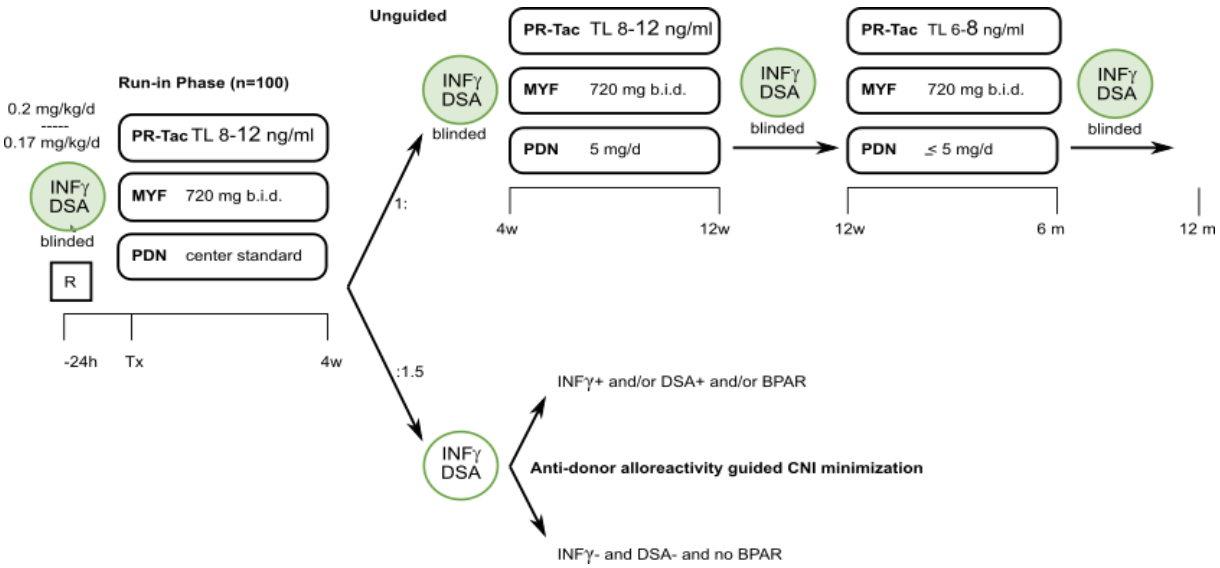

Figure 1: Run-In Randomization and Treatment

After a run-in phase of 4 weeks, patients are randomized to either receive an unguided standard therapy or an immune-guided CNI minimization therapy. PR-Tac = prolonged release tacrolimus (Advagraf® or Envarsus®, should not be switched after study start); MYF=Myfortic, PDN=Prednisolone, R=Randomization

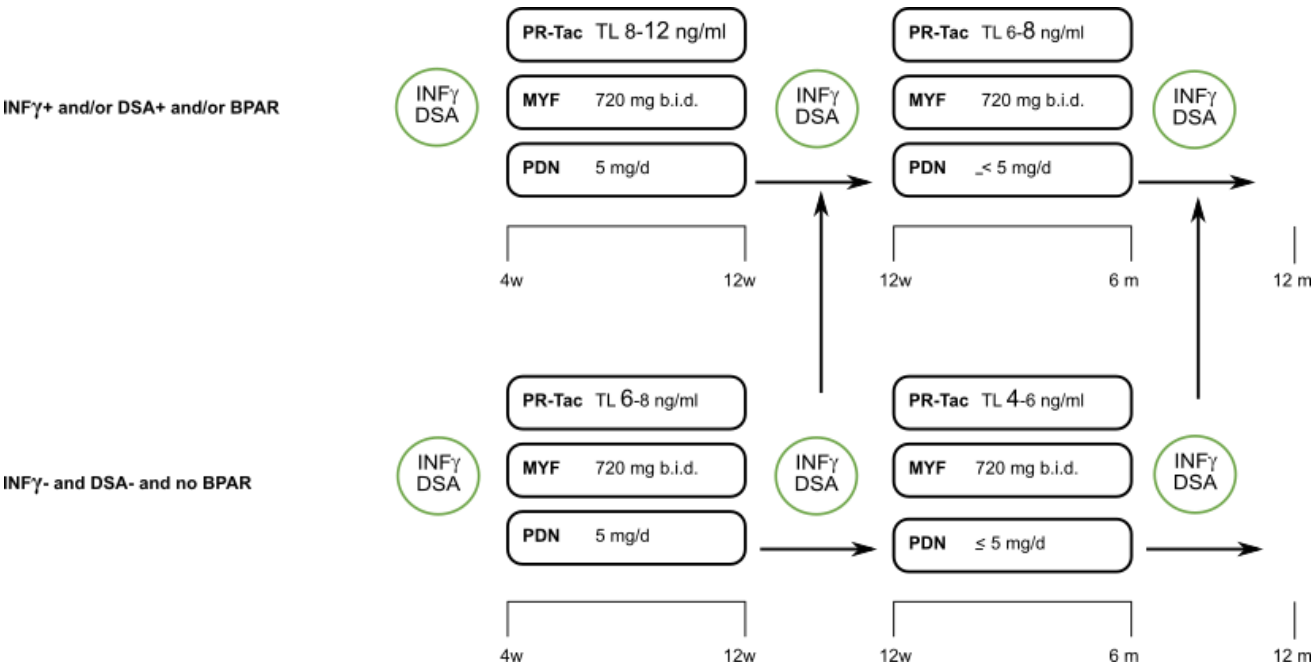

Figure 2: Treatment stratified by the immunological response determined by BPAR, INFγ and DSA

9.2 Discussion of the Study Design, Incl. the Choice of Control Groups

9.2.1 Rationale for Study Design

The controlled parallel group study design is well-established in de novo renal allograft recipients to evaluate an immunosuppressive drug regimen versus current standard treatment. This trial uses the same study drug in all treatment arms. The target levels will be kept different. Thus, blinding is not possible. The primary endpoint graft function (eGFR) as well as the traditional efficacy endpoints e.g., treated biopsy-proven acute rejection, with or without clinical outcomes (i.e. death and graft loss) are well established. The endpoints represent an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while keeping CNI levels low enough to avoid nephrotoxicity.

The higher number of patients in the guided minimization arm accounts for approximately 30% INFγ+ and or DSA+ and/or BPAR patients in the guided minimization arm not eligible for accelerated minimization.

9.2.2 Rationale for Choice of Comparator

Triple therapy, as used in the control arm with tacrolimus, mycophenolate and steroids in recommended doses and trough levels is well established. Donor-specific immune monitoring is not established and will only be used in the study arm for guidance of therapy.

9.2.3 Risk and Benefits

In kidney transplantation there is a medical need for adapted immunosuppressive regimens which maintain the ability to prevent acute rejection while preserving renal function. A regimen that will maintain efficacy while allowing reduced CNI exposure to minimize or avoid CNI-associated adverse reactions (including nephrotoxicity) remains highly attractive. As immunosuppression in both study arms are well established the risks are not increased as compared to centres common practice. CNI minimization to an extent suggested in the study arm is also practiced by our and other centres on a routine basis. The potential risk of a higher rate of acute rejection episodes is well balanced by the close immunological monitoring of patients randomized to the minimization protocol. The benefits for subjects in this trial include improvement in renal function with preservation of graft survival and increased medical monitoring and care. The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria and particular with the immune-monitoring used. In summary we believe that possible benefits will outweigh the risks of the study.

9.3 Selection of Study Population

Subjects must be adult recipients of a primary renal transplant from a living unrelated or living related non-human leukocyte antigen identical donor.

9.3.1 Inclusion Criteria

Patients eligible for study participation will have to fulfil the following requirements:

1. Patient must understand and voluntarily sign an informed consent form including written consent for data protection
2. Male or female subjects ≥ 18 years old
3. Recipients of a primary renal transplant from a living unrelated, living related non-human leukocyte antigen identical donor
4. Must be able to adhere to the study visit schedule and other protocol requirements
5. Male subjects (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in reproductive sexual activity with Females of Childbearing Potential (FCBP) [§] while on study medication and for at least 13 weeks after taking the last dose of study medication. In addition, their female partners should use a highly-effective birth control method.
6. Females of childbearing potential (FCBP)[§] must have a negative pregnancy test during screening and immediately before randomization and must be willing to use a **highly effective**[&] form of birth control when engaging in reproductive sexual activity while on study medication and for at least 6 weeks after taking the last dose of study medication

§) A female of childbearing potential (FCBP) in the context of this study is a sexually mature female following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

&) Highly effective contraception: methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. The following contraceptive methods are regarded as highly-effective: Use of an intrauterine device (IUD), or sterilized male partner (with appropriate post-vasectomy assessment) as well as true abstinence are accepted as highly-effective single birth control methods. As mycophenolate could reduce the effectiveness of hormonal methods all hormonal methods must be used with a barrier method.
Examples of non-acceptable methods of contraception include: periodic abstinence (e.g. calendar, symptothermal, etc.), withdrawal (coitus interruptus), or spermicides. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also not considered highly effective.

9.3.2 Exclusion Criteria

Patients with any of the following were excluded:

1. Hypersensitivity to tacrolimus or other macrolides or to any of the components of the planned study treatment
2. Immunized patients with a current PRA > 5%
3. Recipient of ABO incompatible allograft or CDC crossmatch positive transplant

4. Subjects known to be HIV positive and HBsAg and/or a HCV positive subject with evidence of elevated LFTs (ALT/AST levels ≥ 2.5 times ULN). Viral serology results obtained within 6 months prior to randomization are acceptable
5. Recipient of a kidney from a donor who tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV)
6. Subject with severe systemic infections, current or within the two weeks prior to randomization
7. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
8. Subject with white blood cell (WBC) count ≤ 2,000 /mm3 or with platelet count ≤ 50,000 /mm3 at randomization
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive ß-HCG laboratory test
10. Use of any other investigational medication within 30 days prior to transplantation or 5 half-lives if known (whichever is longer)
11. Missing written informed consent of kidney donor or recipient
12. Have participated in this study before
13. Patients who are possibly dependent on the sponsor or the investigator

9.3.3 Removal of Patients from Therapy or Assessment

9.3.3.1. Individual Patients

Possible reasons for study treatment discontinuation are:

- Adverse event
- Lack of efficacy
- Technical problems
- Subject/guardian decision

The investigator should discontinue subjects from their randomized treatment regimen if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

If, at any time throughout the study, the randomized treatment regimen or any component of the regimen is interrupted for longer than 21 consecutive days, unless being held due to an elective surgical procedure then the patient is no longer considered to receive the randomized treatment.

In individual patients (e.g., inability to achieve target levels) Advagraf® or Envarsus® can be substituted by non-prolonged release tacrolimus in line with the randomized treatment.

Subjects who discontinue the randomized treatment shall attend their follow up visits after 4 and 12 weeks, and after 4 and 12 months anyhow.

Patients are off study (=premature study termination) for the following reasons:

- Lost to follow-up
- Death
- Graft Loss

End of study documentation including date and reason has to be completed in case of premature study termination.

9.3.3.2. Study as a Whole

The BfArM and the IEC have the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

The sponsor reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data;
- Unsatisfactory enrolment with respect to quantity or quality;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (e.g., IRB/IEC, regulatory authorities).

9.4 Treatments

9.4.1 Treatments Administered

Advagraf® or Envarsus® (tacrolimus extended release (ER), also known as FK-506) is the investigational drug in this study.

Advagraf® and Envarsus® are used within the approved indication and will be prescribed at the expense of the statutory health insurance (GKV). According to §5(8) GCP-V no extra labelling was required.

9.4.1.1. Dose and Dose Interval

Subjects will take prolonged-release tacrolimus once daily in 24 h intervals, on a constant schedule with regards to time of day and relation to meals. Prolonged-release tacrolimus is started 24 h prior transplant at a dose of 0.2 mg/kg/d Advagraf® or 0.17 mg/kg/d Envarsus® and thereafter administered according to the randomized treatment plan with the initially chosen formulation until end of study at 12 months post transplantation.

9.4.1.2. Treatment Arms

Control arm: Living donor kidney transplant recipients receive a standard dose CNI-based immunosuppression with prolonged-release tacrolimus (Advagraf® or Envarsus®) + EC mycophenolic acid (720 mg bid as tolerated) + prednisolone (according to centre practice). Prolonged-release tacrolimus is introduced 24 h prior to transplantation at a dose of 0.2 mg/kg/d Advagraf® or 0.17 mg/kg/d Envarsus®. The target trough level for the first 12 weeks is 8-12ng/ml. At 12 weeks prolonged-release tacrolimus will be tapered further down to 6-8 ng/ml. Investigators are encouraged to keep trough levels - whenever possible - in the upper target range. Steroids are tapered by centre standard to a minimum dose of 5 mg prednisolone (or equivalent) at 4 weeks after transplantation.

CNI minimization guided by immune monitoring: Living donor kidney transplant recipients receive a standard dose CNI-based immunosuppression with prolonged-release tacrolimus (Advagraf® or Envarsus®) + EC mycophenolic acid (720 mg bid as tolerated) + prednisolone (according to centre practice). Prolonged-release tacrolimus is introduced 24h prior transplantation at a dose of 0.2 mg/kg/d Advagraf® or 0.17 mg/kg/d Envarsus®. Tacrolimus trough level for the first 4 weeks are 8-12 ng/ml. At 4 weeks (as soon as DSA/INFγ results become available) prolonged-release tacrolimus will be tapered further down to 6-8 ng/ml. In case of a BPAR and/or an INF-γ Elispot shows a donor-specific T-cell reactivity above threshold and/or the LUMINEX single antigen bead assay confirms the presence of donor-specific antibodies, CNI reduction is withheld. Based upon negative assays at 12 weeks immunosuppression is further reduced to a tacrolimus trough level of 4-6 ng/ml. Investigators are encouraged to keep trough levels – whenever possible - in the lower target range. At 6 months the immunological parameters are controlled again. Positivity in one of the assays (DSA or INFγ) or a BPAR triggers an incremental increase to the next higher immunosuppressive tacrolimus trough level range. Steroids are tapered by centre standard to a minimum dose of 5 mg prednisolone (or equivalent) at 4 weeks after transplantation.

9.4.2 Identity of Investigational Products

Advagraf® is supplied as prolonged-release hard capsules containing tacrolimus.Name: Advagraf®; EMEA Product number: EMEA/H/C/000712

Marketing Authorization Holder: Astellas Pharma Europe B.V.

Date of issue of Market Authorization valid throughout the European Union: 23-Apr-2007

Advagraf® is available in 0.5, 1.0, 3.0 and 5.0 mg capsules. Excipients with known effect: Lactulose, trace amounts of soya lecithin. For the full list of excipients see the Summary of Product Characteristics (SmPC).

Envarsus® is supplied as prolonged-release tablet

Name: Envarsus®,

EMEA Product number: EMEA/H/C/002655

Marketing Authorization Holder: Chiesi Farmaceutici S.p.A

Date of issue of Market Authorization valid throughout the European Union: 18.07.2014

Envarsus® is available in 0.75, 1, and 4 mg tablets. Excipients with known effect: Lactose (monohydrate). For the full list of excipients see the Summary of Product Characteristics (SmPC).

Active substance of both products: tacrolimus

INN or common name: tacrolimus

Therapeutic area: Graft Rejection

ATC code: L04AD02

Dosage From

Prolonged-release hard capsules (Advagraf®) and prolonged release tablets (Envarsus®).

9.4.3 Method for Assigning Patients to Treatment Groups

Randomization will be performed at the baseline visit after checking for inclusion/exclusion criteria and prior to transplantation. Randomization will occur with sealed envelopes in a 1:1.5 ratio to either unguided control or guided accelerated minimization therapy. Investigators have to use the envelopes in a strictly ascendant order according to the randomization number printed on the front. If the randomization envelope is opened, the screening number and the date must be written on the envelopes and signed by the investigator or a person responsible for randomization. The resulting treatment arm and the randomization number will be noted in the screening log and the eCRF immediately. Under no circumstances should an investigator discard an envelope. All randomization envelopes are subject to monitoring and will be returned to the sponsor at the end of the study.

9.4.4 Management of Tacrolimus Targets

The first target trough level is determined on postoperative day 1 after a total of 2 intakes of medication. Thereafter, 3 times a week (Mo, We, Fr) and if indicated in inpatients. Outpatients will be monitored weekly for the first 6 weeks, every other week between week 6 and 12 after transplantation and every 4 weeks within the first year. In case of a dose change trough levels will be closely monitored weekly until stable trough levels are achieved.

9.4.5 Blinding

This is an open label study, and no blinding has been done.

9.4.6 Prior and Concomitant Therapy

Mycophenolate and steroids are elements of the standard immunosuppressive regimen and are the same in both treatment arms. Therefore, they are considered background medication. Their doses are to be reported as integral part of the immunosuppressive treatment on the eCRF.

Subjects may take any medication that would not be expected to interfere with the conduct of the study.

Concomitant medication will be recorded for continuous medication and medication considered relevant for the interpretation of study results including antibiotic, anti-mycotic, and anti-viral treatments, vaccinations, treatments for acute rejections or adverse events. Records contain the dose, and start and end date when the medication was taken.

9.4.7 Treatment Compliance

No drug accountability checks were implemented as prescribed medications were used. The implementation of dosing steps had to be recorded in the source documents and had to be entered in the eCRF. Worksheets were provided to document the decision for each dosing step according to the standard in the control group or in response to immunological results in the immune monitoring guided arm. Measurement of tacrolimus target through levels was defined in the study protocol (section 9.4.4).

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The efficacy assessments during the treatment phase of the study will be done at the intervals specified in the Schedule of Assessments (Table 1).

9.5.1.1. Flow Chart

Table 1: Schedule of Assessments

Study period	Screening		Run-in			Randomized Treatment			
Visit	SCR	BL	W1	W2	W3	W4	W12	M6	M12
Time frame	-6m	-24h	1w±3d	2w±3d	3w±3d	4w±1w	12w±2w	6m±1m	12m±1m
Informed consent	Routine pre-Tx assessments	x							
Demographics (gender, race)		x							
Medical History		x							
Inclusion/ Exclusion		x							
Randomization		x							

Study period	Screening		Run-in			Randomized Treatment			
Visit	SCR	BL	W1	W2	W3	W4	W12	M6	M12
Time frame	-6m	-24h	1w±3d	2w±3d	3w±3d	4w±1w	12w±2w	6m±1m	12m±1m
Vital signs (HR, RR, Weight, Height)		x	A	A	A	x	x	x	x
Physical exam		S							S
PR-Tac dose		x	A	A	A	A	A	A	A
TAC trough level			A	A	A	A	A	A	A
MPA dose		x	A	A	A	x	x	x	x
ST dose		x	A	A	A	x	x	x	x
Central laboratory		x	A	A	A	x	x	x	x
Pregnancy test		x				x	x	x	x
DSA Luminex		x				x	x	x	x
INFγ Elispot		x				x	x	x	x
Donor Sample		x							
BPAR			as needed						
Hospitalization				as needed					
AEs		as needed							
SAEs		as needed							
Concomitant medication			x	as needed					x
Donor specific DNA		x				x		x	x

Legend to Schedule of Assessments:
X=assessment for all subjects in study regardless of on or off randomized study regimen, to be recorded in clinical data base
A=assessment ONLY for subjects maintaining their randomized study regimen, to be recorded on clinical data base (for patients withdrawn from randomized treatment, immunosuppressive treatment is to be recorded at visits w4, w12, M6, and M12)
S=assessment to be recorded on source documentation only

1. Informed consent should be obtained prior to performing any study-related procedures which is expected when the patient arrives for the transplantation visit. Screening with routine assessments may extend up to 6 months prior transplant.
2. The Run in phase covers the transplant period from 24 h prior to surgery until start of randomized treatment at 4-6 weeks after transplantation.
3. Visit scheduling refers to the time of assessments. At visits W4, W12, M6, and M12 this is when a blood sample for immunological monitoring is taken. Immune-guided adjustment of TAC dosing may occur within 2 weeks after the scheduled visit W4, W12, and M6.
3. Randomization must occur prior to transplantation.
4. Central laboratory tests indicated at each visit include: Biochemistry (sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, urea, creatinine, uric acid, CRP, AST, ALT, γ-GT, alkaline phosphatase, total bilirubin, CPK, lipase and amylase, INR, PTT); Hematology (platelets, hemoglobin, red blood cell (RBC), white blood cell (WBC) and differential count); Lipids: total cholesterol, HDL, LDL and triglycerides. Urinalysis (leukocytes, nitrite, protein, creatinine, albumin, glucose; proteinuria and albuminuria per 24hr period will be estimated from spot protein/creatinine and albumin/creatinine ratios).
5, Serum or urine pregnancy testing for ß-HCG using an assay with a sensitivity of at least 25 mIU/mL is to be done on females of childbearing potential prior to randomization and in 4 weeks intervals after transplantation until end of the study.
6. All serious adverse events, serious infections and pregnancies must be reported from informed consent until 30 days after the last study visit post randomization (i.e. to the month 12 visit or early discontinuation from study).

9.5.1.2. Description of Assessments

The following assessments will provide outcome data.

9.5.1.2.1 Assessment of Efficacy

Renal Function

Renal function will be determined by eGFR calculated according to the 4-variable MDRD formula which estimates GFR using four variables: serum creatinine, age, ethnicity, and gender. Therefore, year of birth, ethnicity and gender are to be recorded at the screening visit. Serum creatinine and urea are recorded as part of the laboratory assessments at the baseline and subsequent visits (BL, W1, W2, W3, W4, W12, M6, and M12).

BPAR

Suspected acute rejection episodes are assessed throughout the study. Regardless of anti-rejection treatment, an allograft biopsy must be performed within 48 h. All episodes of acute rejection will be immediately recorded in the eCRF together with start date, Banff grading according to the current 2013 update and anti-rejection treatment.

Graft Loss and Death

During the study period all cases of graft loss (equivalent to need of dialysis for at least 6 consecutive weeks; allograft was presumed lost on the day the patient started chronic dialysis) or death are reported in the eCRF together with date and reason.

9.5.1.2.2 Assessment of Safety

9.5.1.2.2.1 Adverse Events

A qualified physician associated with the study will be available to assess clinical signs and symptoms that may be indicative of an adverse event. All physical examination findings, vital sign abnormalities, and clinical laboratory abnormalities will be captured as AEs when deemed medically significant by the investigator. Adverse events will be assessed during all post baseline visits except the screening visit. Both spontaneous as well as prompted reports of AEs will be recorded.

Special attention will be paid to onset of infections or malignancies, as well as hypertension, diabetes, hyperlipidaemia, and proteinuria.

9.5.1.2.2.2 Vital Signs

Vital signs (HR, RR, weight) will be recorded in the eCRF at all visits for patients on the randomized study medication. Height will be measured at screening only. After a patient was withdrawn from the tacrolimus regimen, vital signs will be captured only at 4 and 12 weeks, and after 6- and 12-months post transplantation.

9.5.1.2.2.3 Laboratory Variables

According to the protocol blood samples taken during visit 1 to visit 8 should be sent to the individual laboratories of the investigators and normal values from each laboratory should be provided before study start.

Central laboratory tests indicated at each visit include: Biochemistry (sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, urea, creatinine, uric acid, CRP, AST, ALT, γ-GT, alkaline phosphatase, total bilirubin, CPK, lipase and amylase, INR, PTT); Haematology (platelets, haemoglobin, red blood cell (RBC), white blood cell (WBC) and differential count); Lipids: total cholesterol, HDL, LDL and triglycerides. Urinalysis (leukocytes, nitrite, protein, creatinine, albumin, glucose; proteinuria and albuminuria per 24hr period will be estimated from spot protein/creatinine and albumin/creatinine ratios).

Serum or urine pregnancy testing for ß-HCG using an assay with a sensitivity of at least 25 mIU/mL is to be done on females of childbearing potential prior to randomization and in 4 weeks intervals after transplantation until end of the study.

9.5.1.2.3 Other Assessments

9.5.1.2.3.1 Blood Samples

Blood samples are required from donor and recipient as outlined in the Schedule of assessments (Table 1).

Donor sample: A blood sample of about 125 ml is required from the donor at baseline to be sufficient for the immunological assessments throughout the study. The sample will be frozen on arrival in the laboratory for later uses (for tissue typing and transplant immunology). In case of sampling errors or technical difficulties any effort should be made to gain another sample.

Recipient sample: Recipient samples (35 ml) are taken at baseline, week 4, week 12, and 6 and 12 months after transplantation. These samples are immediately sent to the laboratory where analysis will be performed.

Therefore, it is crucial that all visit dates are subject to due coordination with the laboratory.

9.5.1.2.3.2 DSA Luminex

Patient sera are screened for the presence of alloantibodies against HLA-class I and II by means of Luminex (One lambda LabScreen, USA) prior to transplantation (baseline) and at 4 weeks, 12 weeks, 6 months and 12 months after transplantation. Positively screened patients are measured by Single Antigen Beads to identify allele-level antibodies. The antibody specificity in relation to the donor is confirmed if MFI (mean fluorescence intensity) is higher than 3000.

9.5.1.2.3.3 INFγ Elispot

The highly sensitive INF-γ Elispot assay (enzyme-linked immunosorbent spot assay) will be performed as recently described by Bestard et al. 2013 (8). Briefly, $3x10^5$recipient PBMC will be stimulated with T-cell depleted (Rosettesep, StemCell Technologies, Madrid, Spain), irradiated (30Gy-18mins) donor PBMC ($3x10^5$) for 24 hours in duplicates or triplicates in activated and precoated (capture antibody: capture mAb 1-D1K <IFN-γ> (Mabtech AB Sweden, Code #3420-3) Elispot plates (MAIPN 4550, Millipore). After addition of the detection antibody (mAb <IFN-γ>-Biotin7-B6-1 (Mabtech AB Sweden, Code #3420-6) and visualization with Streptavidin-HRP (Mabtech AB Sweden, Code #3310-09) and "ready to use substrate" (Mabtech AB Sweden, Code #3651-10) the resulting spots will be counted on a computer-assisted enzyme-linked immunospot image analyzer (C.T.L. Europe GmbH-Bonn). The frequencies of allospecific- INF-γ producing T-cells will be expressed as the number of cytokine-producing spots per $3x10^5$ recipient PBMC. Irradiated recipient PBMC (autologous control) and irradiated third party PBMC will be used for controls; >25 spots / $3x10^5$ responder PBMC will be defined a positive test. Recipient cells will be harvested at five different time-points (pre-TX, and W4, W12, M6, M12 post TX). The INF-γ Elispot assay is well established and part of the clinical routine. The assay will be performed in the laboratory for tissue typing and transplant immunology.

9.5.1.2.3.4 Donor-specific DNA

Assessments for donor-specific DNA are performed at the baseline visit, 4 weeks, 6 months, and 12 months after transplantation.

The AlleleSEQR Chimerism Assay (Celera/Abbott) is used for detection of circulating donor specific DNA. Before transplantation donor and recipient genotypes are identified by realtime PCR and screened for insertion or deletion polymorphism in 34 loci over 20 chromosomes. A detected polymorphism in donor DNA but not in recipient DNA is called an informative marker. The likelihood of more than 2 informative markers between two individuals is above 99.8%. In a second step the informative marker is used to detect and quantify circulating donor specific DNA in the peripheral blood of the recipient after transplantation. The chimerism analysis is performed in duplicates on post-transplant recipients DNA samples. The pre-transplant donor DNA sample will be analysed in parallel to evaluate the relative amount of donor DNA within recipient blood which will be expressed as a percentage of donor DNA in the post-transplant recipient sample.

9.5.2 Primary Efficacy Variable(s)

The primary endpoint is the renal function at 12 months after transplantation determined as eGFR calculated by the MDRD-4 formula.

9.5.3 Secondary Efficacy Variables

Secondary endpoints are:

- Proportion of patients with graft loss at 12 months after transplantation
- Proportion of deaths within 12 months
- Overall survival (time between transplantation and death)
- Graft survival (time between transplantation and graft loss or death)
- Death censored graft survival (time between transplantation and graft loss; deaths with functioning graft will be censored)
- Incidence of BPAR/tBPAR by severity (Banff classification 2013 Update [9]) and time to event
- Proportion of treatment failures based on any of the following: graft loss or death, BPAR, switch to another immunosuppressive regimen, or lost to follow up and related time to event data
- Composite efficacy failure rate of tBPAR, graft loss or death and eGFR (MDRD-4) < 50 ml/min/1.73m2 at 12 months post transplantation
- Renal function at 12 months by creatinine, CKD-Epi, Nankivell, and Cockroft-Gault formulas
- Loss of renal function (Creatinine, MDRD-4, CKD-Epi, Nankivell, Cockroft-Gault) during randomized treatment between week 4 and end of study (at 12 months)
- Proportion of patients with creatinine > 1.5 resp. > 2.0 mg/dl at 12 months
- Proportion of patients with eGFR (MDRD-4) < 50 ml/min/1.73m2 at 12 months
- Proportion of patients with creatinine change > 0.3 mg/dl between 3 or 6- and 12-months post transplantation
- Proportion of patients with eGFR (MDRD-4) decline > 10 ml/min/1.73m2 between 3 or 6- and 12-months post transplantation

Additional analysis is undertaken on the per protocol population and for the comparison of the unmonitored group to the allo-response guided CNI minimization group, negative for BPAR, DSA and INFγ.

9.5.4 Further Exploratory Endpoints

Further endpoints are:

- Incidence of donor reactive antibodies (DSA) at 12 months
- Incidence of cellular donor reactivity (INFγ) at 12 months

- Incidence of immune adaptation defined as donor to third party reactivity at 12 months
- Incidence of circulation donor derived DNA at 12 months
- Presence and levels as well as the course of DSA, INFγ, and donor specific DNA

Additional exploratory analysis may be specified in the statistical analysis plan.

9.5.5 Safety Parameters

Safety parameters are:

- Type, frequency, and severity of adverse events and relationship to tacrolimus
- Incidence of infections or malignancies
- New onset of hypertension, diabetes, and hyperlipidaemia
- Incidence of serious adverse events
- Number of subjects who prematurely discontinue study medication due to any adverse event

9.5.6 Drug Concentration Measurements

For tacrolimus target through level management as described in section 9.4.4 tacrolimus through level were analysed in the local laboratory. The through levels were reported in the eCRF at each visit.

9.6 Data Quality Assurance

9.6.1 Study Conduct and Monitoring

The sponsor ensures that appropriate monitoring procedures are performed before, during, and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator(s) and the staff. Prior to enrolling subjects into the study, a sponsor representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs with the investigator(s). Monitoring will include on-site visits with the investigator(s) and his/her staff as well as any appropriate communications by mail, fax, or telephone. Data quality is monitored on a continuous basis and deficiencies clarified via online queries. At each monitoring visit, the facilities, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the sponsor's representative for adherence to the protocol and GCP.

At each site visit, the monitor will review eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRF against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator(s) and/or his/her staff. Any necessary corrections will be made directly to the eCRFs by the investigator(s) and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and the proper

recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

9.6.2 Data Entry and CRF-Review

For each patient enrolled, an electronic Case Report Form (eCRF) must be completed and signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated).

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

9.6.3 Final Data Quality Assurance

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against investigator's records by the study monitor (source document verification). The data collected will be entered into the study database, where plausibility checks are executed automatically during data entry. Before data analysis are conducted, a comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator.

All arguable questions about the interpretation of data were decided before data analysis and were fixed in the Data Review Report.

For each stage of import or export of data, performed for the purpose of processing the data for distribution analyses, statistical tests, design of figures etc., the identity of data was controlled and validated.

9.6.4 Software Used

Data entry was performed using ACTM.DC the data input program of the Algora Clinical Trial Management system. The database behind was Microsoft SQL-Server 7.0.

The SAS software version 9.4 will be used for the statistical analysis and for the reporting of this trial. Additional graphics may be provided by the use of the R package (version 4.1.2).

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

9.7.1 Statistical and Analytical Plans

A statistical Analysis Plan should be prepared, and a Blind Review should be conducted before unblinding the study.

A detailed statistical analysis plan will be prepared and finalized prior to the analysis. Formal records shall be kept of when the statistical analysis plan was finalized.

Prior to the analysis, possible protocol violations will be classified as “severe” (lead to exclusion from ITT and PP), “major” (lead to exclusion from PP), and “minor“ (no exclusion) in a blinded review process. Patients will be allocated to the individual data sets with regard to the classification of possible protocol violations. The final data sets shall be described in detail in a blind review report. Any deviations from the planned statistical analysis have to be discussed in the final study report.

9.7.1.1. Statistical Methodology

Based on the common active substance of both prolonged release formulations, the primary analysis will be done according to the intent-to-treat principle for the whole study population (Intent to treat population as defined in 9.7.1.2) including patients who received Advagraf® and patients who received Envarsus®. In addition, a combined per-protocol analysis will be prepared. Analyses of patients for each prolonged release formulation of tacrolimus is planned as secondary analysis.

All relevant parameters will be evaluated in an explorative or descriptive manner, providing mean, median, range, standard deviation and/or 95% confidence interval for continuous variables and frequency tables for categorial or binomial variables. If p values are calculated in these analyses, they will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. All p values will be two-sided if not stated otherwise. Comparisons between treatment groups will be performed applying Fishers Exact Test for categorial (dichotomized) or binomial variables and Wilcoxon ranks sum tests for numerical outcome variables. Analysis of covariance (ANCOVA) will be applied to continuous renal function parameters. Time to event data will be analysed by the Kaplan-Meier method and between-group comparisons will be performed using the Cox-proportional hazards model.

If p values are calculated in the area of explorative analysis, they will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. All p values will be two-sided if not stated otherwise.

9.7.1.2. Datasets to be analysed

All data will be analysed, except data of patients who have withdrawn consent.

All deviations from the study plan as specified in the protocol have to be reported and will be listed in the blind review report. It is the responsibility of the sponsor to rate these deviations according to the following classification:

- Minor: minor impact on study result; does not result in exclusion of any analysis population
- Major: may have some influence on study results; results in exclusion from the PP population but remains evaluable for the ITT population.
- Severe: is considered to produce severe bias of the study result; will be excluded from both the PP and the ITT population. Exclusion from the ITT population requires extra justification.

Recorded distinctive features that are considered in accordance with the protocol by the sponsor will be rated as “none”. These cases will not appear in the final report.

Intent to Treat Population

Intent-to-treat population (ITT) is defined to include all patients who are randomized and transplanted, and who had no severe protocol violation.

The ITT population is the primary data set to be analysed for this study.

Per Protocol Population:

The per protocol population is defined to include the intent-to treat population excluding patients

- with missing and/or inadequate measurements for immune monitoring
- who switched to another immunosuppressive regimen
- with major violation of inclusion-/exclusion criteria, or
- who have other major protocol violations

Safety Population:

The safety population is defined to include all patients who signed the informed consent, received at least one dose of the trial medication and have a safety follow-up. Patients will be included in the safety population regardless of whether they are randomized or prematurely withdrawn.

9.7.2 Determination of Sample Size

The sample size calculation has been conducted with respect to the primary endpoint (the eGFR MDRD-4 12 months after transplantation). The question is whether the guided CNI minimization will lead to an improved renal function compared to the standard procedure. For sample size calculation a median difference in eGFR of 10 ml/min/1.73m2 with a common standard deviation of 16 ml/min/1.73m2 between the unguided and the guided accelerated minimization group is assumed. A drop-out rate of 10% is calculated for the entire study period including the run-in phase. Based on our study population we assume a 2:1 distribution of patients that fall in the group negative for BPAR and INFγ and DSA group and the group positive for BPAR or INFγ or DSA in the study arm. Therefore a 1.5-fold number of subjects shall be randomized to the guided CNI minimization compared to the standard treatment. Based on this and a power of 0.8, and alpha = 0.05 the total number of patients required is 90. Accounting for dropouts a total of 100 subjects are to be included, 60 into the guided minimization arm and 40 into the control group.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes to the Conduct of the Study

The 2nd final of the study protocol dated 28-JAN-2016 provided the bases for regulatory approval of the study. In this version Advagraf® was the investigational product to be used. With amendment 1, dated 30-Jan-2019 it was introduced that future patients should be treated with Envarsus®. Advagraf® and Envarsus® both contain the active substance Tacrolimus and are comparable prolonged release formulations and both had a marketing authorization for the study indication. Therefore, interchangeable use of both was justified.

With this change in the protocol, it was defined that patients already treated with Advagraf® and the patients to be treated with Envarsus® should be analysed together as the primary analysis population. Sub-populations of patients according to the product used should be analysed separately to confirm the postulated homogeneity of the results.

Due to difficulties in study conduct and recruitment, further enhanced by the pandemic situation with COVIUD-19, it was decided to stop recruitment prematurely on 20-APR-2020. Already included patients remained in the follow up until their regular 12 months visit. The study end then occurred with the last patient last visit (LPLV) on 05-FEB-2021.

9.8.2 Changes to the Planned Analysis

Besides the protocol changes implemented with amendment 1 the statistical analysis plan was adapted also taking into account the situation after premature termination of the trial. In the final SAP the following changes were implemented.

During the data review process some analyses became obsolete due to the lack of necessary data:

- Analysis of donor derived DNA (no donor derived DNA was detected)
- Analysis of death and graft survival (no patients reported graft loss or death)
- Multiple imputation procedures (no missing renal function data after 12 months)

Due to premature termination of the study a simplified analysis procedure should be applied due to the fact, that some analyses are not considered very meaningful with the small amount of data. In these cases, listings should be provided instead.

- Level analysis of DSA
- Analysis of patient subgroup with DSA-/INF-/BPAR-

The planned sub-group analysis be eGFR on day 1 after transplantations according to cut-offs of < 45 or y 60 ml/min/1.73m^2 is not considered appropriate and will be omitted in the final report.

Sub-group analysis according to treatment with Advagraf® or Envarsus® is no longer considered adequate, because patients switched between Advagraf® and Envarsus®. Considering Amendment 1 it was decided to analyse the subgroups according to the underlying contract with Astellas or Chiesi.

10 STATISTICAL/ANALYTICAL ISSUES

The statistical analysis was planned after completion of the trial, which is when all patients had completed their follow up phase. This final analysis therefore includes all efficacy and safety data until end of study.

Statistical analysis is based on the final statistical analysis plan, dated 07-FEB-2022 which is available in the appendix.

If p values are calculated in the area of explorative analysis, they should be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing should be performed. All p values should be two-sided if not stated otherwise.

10.1 Primary Efficacy Criterion

Among various measures of renal function, the MDRD-4 formula has been selected for the primary endpoint. The parameter to be tested will therefore be the eGFR calculated by the MDRD-4 formula at 12 months after transplantation.

The 4-variable MDRD formula estimates GFR using the four variables: serum creatinine, age, ethnicity, and gender (Version 2000 [10]):

$eGFR_{12M}$ (ml/min/1.73 m2) = 186 * Serum Creatinine (mg/dl)$^{-1.154}$
* age$^{-0.203}$
* [1.210 if black]
* [0.742 if female]

(Creatinine levels in µmol/l can be converted to mg/dl by dividing them by 88.4)

This formula delivers values in ml/min/1.73 m^2 and no further adaption to body surface is necessary

The trial tests the null hypothesis that there is no difference in eGFR at 12 months after transplantation versus the alternative hypothesis that there is a difference in eGFR between the CNI minimization group and the unguided control.

H0: $eGFR_{12M}$(CNIminimization) = $eGFR_{12M}$(Control)
HA: $eGFR_{12M}$(CNIminimization) ≠ $eGFR_{12M}$(Control)

The difference will be tested by means of the Wilcoxon rank sum test. $P < 0.05$ will be considered statistically significant (this is, H0 will be rejected if $P(H0) < 0.05$).

10.2 Secondary Efficacy Criteria

The primary parameter should be analysed in an exploratory manner for the per-protocol population using the above-described methodology.

Furthermore, the secondary efficacy parameters should be analysed in an exploratory manner using descriptive statistics, confidence intervals and test-statistics. Non-parametric procedures should be preferred for all scores but parametric processes may support the evaluation when justified by the nature of the distribution.

Endpoints related to renal function will be evaluated according to Cockroft-Gault, Nankivell, CKD-Epi formulas using the same methodology as described for the primary analysis. Serum creatinine will be analysed respectively.

The following formulas will apply [11].

Cockroft-Gault [12]:

CrCl [ml/min] = (140 – age) x (body weight in kg)/(72 × SCr) × 0.85 (if female)
SCr in mg/dl

or:
CrCl [ml/min] = (140 – age) x (body weight in kg)/(0.82 × SCr) × 0.85 (if female)
SCr in µmol/l

Nankivell [13]:

GFR = 6.7/SCr + 0.25 × weight – 0.5 × urea – 100/height^2 + 35 (or 25 if female)
SCr in mmol/l, weight in kg, urea in mmol/l, height in m

Calculated values for Cockroft-Gault and Nankivell have to be adjusted to 1.73m^2 body surface.
GFR (ml/min.*1.73 m^2) = GFR * 1.73 / BS

As body surface has not been recorded the formula of Mosteller[14] will be applied:

BS = SQRT(Height [cm] x Weight [kg] / 3600)

CKD-EPI (2009) [15]:

GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1) –
1.209 × 0.993Age × 1.018 [if female] × 1.159 [if African American]

where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr/κ or 1, and
max indicates the maximum of Scr/κ or 1
The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

Treatment failure is defined as having at least one of the following events:

- Graft loss, or
- Death, or
- BPAR, or
- Switch to another immunosuppressive regimen, or are
- Lost to follow up

Composite efficacy failure rate based on the following: tBPAR, graft loss or death, and eGFR (MDRD-4) < 50 ml/min/1.73m^2 at 12 months post transplantation

Biopsy proven acute rejection (BPAR) was defined as either a T cell-mediated rejection (including a borderline rejection) or an antibody mediated rejection (according to the Banff 2013 criteria).

The incidence of endpoints such as acute rejection, BPAR/tBPAR, graft loss, death, as well as composite endpoints such as treatment failures and the composite efficacy failure rate will be estimated by use of the Kaplan-Meier method. All time variables will be relative to the day of transplantation.

All p values from the statistical tests in the area of explorative analysis, which exceed the primary target criterion during the testing, should only be explorative explained; this means they do not serve to confirm the previously proposed hypotheses.

10.3 Analysis of Safety Data

Adverse events (AE) will be coded using MedDRA version 19.1 and will be analysed by the MedDRA coded event term on the PT and SOC level. The severity will be graded mild, moderate, severe, very severe and the causal relationship to the study product will be assessed as related or not related.

The laboratory data should be presented using descriptive statistics as well as using shift-tables with respect to normal ranges.

Previous medication and concomitant medication should be encoded using the ATC dictionary. Frequency tables will be compiled based on the encoding for the medication.

10.4 Confirmatory Analysis (or Primary Analysis)

The confirmatory analysis is based on the ITT population. A detailed analysis plan is given in the Study Protocol amendment 1, dated MMM DD, YYYY and elaborated with the final statistical analysis plan dated 30-JAN-2019.

The primary analysis had been defined as a test for superiority of the test group as compared to the reference group applied on eGFR calculated by the 4-variable MDRD equation.

The analysis procedure chosen is the Wilcoxon rank sum Test. The confirmatory analysis and the rejection of the null hypothesis are based on the calculated P-values only. $P < 0.05$ will be considered statistically significant (this is, H0 will be rejected if $P(H0) < 0.05$). Two-sided confidence intervals that correspond to the statistical tests are presented.

10.5 Supportive Analyses

For sensitivity analysis the following supporting analysis will be performed:

- The primary analysis will be repeated for the per protocol population,
- ANCOVA analysis with eGFR at baseline will be performed
- eGFR calculated by the MDRD-4 formula at each visit
- A mixed model for repeated measures will be fitted for the period starting at 4 weeks after transplantation until the end of study after 12 months

All following supportive analyses are based on the ITT population.

In addition, eGFR will be summarized by visit and treatment group (with and without imputation of missing values). Absolute and percent changes from day 1 will be calculated as well as changes between week 4 and end of study (at 12 months). Randomized treatment groups will be compared in an explorative manner by use of appropriate tests for paired and two-sample data (t-test, paired t-test, Wilcoxon rank-sum test, Wilcoxon signed-rank test). In addition, the subgroup of patients who completed CNI minimization (patients negative for DSA, INFγ, and BPAR) will be compared to the control accordingly. If appropriate, 95% confidence intervals shall be constructed.

All parameters should be evaluated in an explorative or descriptive manner, providing mean, median, range, standard deviation, and/or 95% confidence interval for continuous variables and frequency tables for categorial or binomial variables.

10.6 Homogeneity Analysis (Exploratory Interpretation)

Homogeneity analyses for baseline are performed for the ITT data set and presented by descriptive statistics (frequencies or means and standard deviation).

The following data transformations were applied:

BMI (kg/m2): according to the following formula is added to the baseline parameters [16]:

BMI = weight [kg] / height [m]^2

The following categories will be applied:

Table 2: BMI classification

Classification	**BMI(kg/m²), Principal cut-off points**
Underweight	<18.50
Normal range	18.50 - 24.99
Overweight	≥25.00
Obese	≥30.00

Source: Adapted from WHO, 1995, WHO, 2000 and WHO 2004.
[absolute and relative frequencies]

CMV-Status (pos./neg.)

Table 3: Combined CMV-Status

Nr.	Patient	Donor
1	+	+
2	+	-
3	-	+
4	-	-
5	.	+
6	.	-
7	+	.
8	-	.
9	.	.

10.7 Adjustments for Covariates

To support the primary endpoint, analysis of renal function at the end of the study will be done by ANCOVA adjusted for the baseline renal function with the value from day 14 is taken for baseline.

10.8 Multiple Comparisons/Multiplicity

Only one primary endpoint has been defined and all other analyses are supportive. Therefore, in general no adjustments for multiple testing will be applied.

10.9 Handling of Dropouts and Missing Values

All patients have completed their study with the 12 months visit resulting in a dataset without missings for the primary endpoint and therefore the multiple imputation method planned in the protocol was not applied.

10.10 Examination of Subgroups

Analysis will be performed stratified by sex (male vs. female), age at transplantation (<60 vs. >= 60 years).

Renal function at day 1 (using thresholds of <45 and <60 ml/min/1.73m2 calculated by the MDRD formula) was planned in the protocol but is not applicable after data review (categories defined are not in a practicable range).

Sub-groups of patients treated with Advagraf® and patients treated with Envarsus® should have been analysed separately. After amendment 1 and after final data review it was decided to analyse patients included under Astellas or Chiesi contract instead, as the initial subgroup definition was not adequate because patients switched between Advagraf® and Envarsus®.

10.11 Interim Analyses and Data Monitoring

Due to difficulties in study conduct and recruitment an Interim analysis was performed with a report dated 24-MAR 2020. This interim report should give an overview on the study conduct and summarize the results of the patient population included under the contract with Astellas. The main goal of this analysis was to summarize the current status and to evaluate parameters to evaluate the study conduct in individual patients. Taking into account the difficult situation caused by the COVID-19 pandemic on 15-SEP-2020 a decision was made to stop further recruitment with at that point the last patient being included on 14-JAN-2020.

10.12 Blind Review and Changes to the Analytical Plan

As this is an open label study a data review has been performed prior to the analysis

The Data Review Report includes the final analysis plan and was finalized before the start of the final analysis. Formal records are kept of when the statistical analysis plan and the data revie report were finalized.

Potential protocol violations were classified as “severe”, “major”, “minor“ or “none” in the data review process. Detailed information on protocol violations and on the development of analysis data

sets are provided int the Blind Review Report in the appendix. The final statistical analysis plan is also attached in the appendix.

During the data review process some analyses became obsolete due to the lack of necessary data. These include

- Analysis of donor derived DNA (no donor derived DNA was detected)
- Analysis of death and graft survival (no patients reported graft loss or death)
- Multiple imputation procedures (no missing renal function data after 12 months)

Due to premature termination of the study a simplified analysis procedure will be applied due to the fact, that some analyses are not considered very meaningful with the small amount of data. In these cases, listings will be provided instead.

- Level analysis of DSA
- Analysis of patient subgroup with DSA-/INF-/BPAR-

The planned sub-group analysis be eGFR on day 1 after transplantations according to cut-offs of < 45 or y 60 ml/min/1.73m^2 is not considered appropriate and will be omitted in the final report.

Sub-group analysis according to treatment with Advagraf® or Envarsus® is no longer considered adequate, because patients switched between Advagraf® and Envarsus®. Considering Amendment 1 it was decided to analyse the subgroups according to the underlying contract with Astellas or Chiesi.

The final report will be prepared for the complete dataset as the main report and the subgroup analysis according to the underlying contract (ASTELLAS or CHIESI) will be provided as two independent appendices.

10.13 Software Used for Statistical Analysis

The SAS software version 9.4 for windows, SAS Institute Inc., Cary, NC was used for the statistical analysis and for the reporting of this trial. Additional figures were prepared by use of the R package (version 4.1.2).

11 STUDY PATIENTS

11.1 Screening, Run-In, Primary Selection of Patients

Between 23-May-2016(First Patient First Visit: Pat # 001) and 14-JAN-2020 (Last Patient First Visit: Pat. # 035) a total of 35 patients were included into the study (Table 4).

The first 28 Patients were recruited under the contract with Astellas and the last patient (pat. #28) included 26-Feb-2019 within this contract. Pat 29 (included 19-Mar-2019) until Pat. 35 (included 14-Jan-2020) were then treated within the contract with Chiesi.
The last patient visit was 05/02/21 (LPLV, pat. 35) and therefore, the study duration was between 23/05/16 (FPFV) until 05/02/21 (LPLV) (1719 days, or 56 months, or 4 years and 8 months).

Table 4: Patient inclusion by date

Visit 1 date

V1DatDt	Frequency	Percent	Cumulative Frequency	Cumulative Percent
23/05/16	1	3.57	1	3.57
31/05/16	1	3.57	2	7.14
14/06/16	1	3.57	3	10.71
14/09/16	1	3.57	4	14.29
29/11/16	1	3.57	5	17.86
17/01/17	1	3.57	6	21.43
24/01/17	1	3.57	7	25.00
14/02/17	1	3.57	8	28.57
21/02/17	1	3.57	9	32.14
09/05/17	1	3.57	10	35.71
11/07/17	1	3.57	11	39.29
07/11/17	1	3.57	12	42.86
14/11/17	1	3.57	13	46.43
21/11/17	1	3.57	14	50.00
05/12/17	1	3.57	15	53.57
09/01/18	1	3.57	16	57.14
06/02/18	1	3.57	17	60.71
10/04/18	1	3.57	18	64.29
24/04/18	1	3.57	19	67.86
08/05/18	1	3.57	20	71.43
22/05/18	1	3.57	21	75.00
26/06/18	1	3.57	22	78.57
03/07/18	1	3.57	23	82.14
21/08/18	1	3.57	24	85.71
13/11/18	1	3.57	25	89.29
22/01/19	1	3.57	26	92.86
12/02/19	1	3.57	27	96.43
26/02/19	1	3.57	28	100.00

(🖫 Tab. 01-01-02).

11.2 Disposition of Patients

The following flow chart displays an overview over the conduct of the study and the evaluable patients.

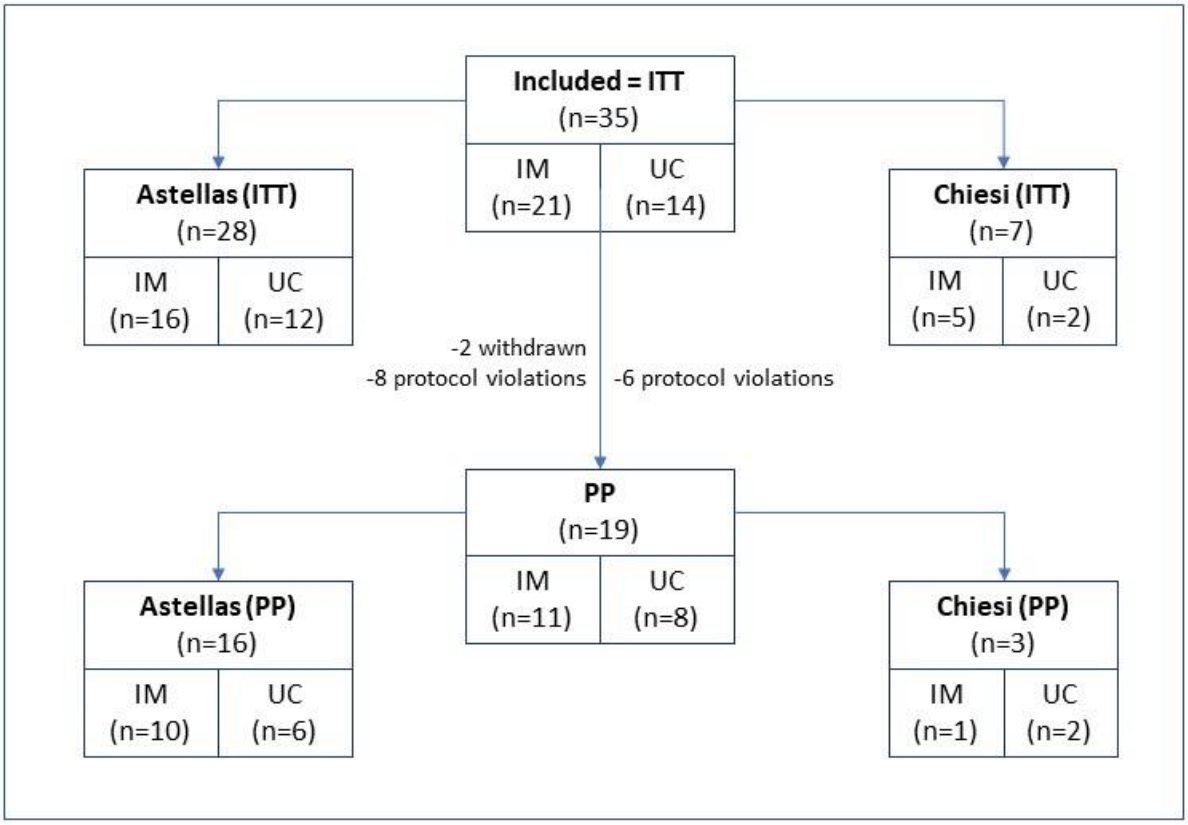

Figure: Study Flow

11.3 Withdrawals and Discontinuations

Only two discontinuations were reported during the trial. Pat. 01: changed to everolimus due to papillary adenoma of the donor kidney and Pat. 20 who had multiple changes of the immunosuppressive regimen and after Banff 3 rejection was switched to Certican+Prograf.

Table 5: List of discontinuations

Patient	Contract	Initial Tacrolimus	Days after Tx	Tacrolimus changed count	Treatment Arm
1	ASTELLAS	Advagraf (ADV)	13	0	IM<ImmuneMonitoring>
20	ASTELLAS	Advagraf (ADV)	58	4	IM<ImmuneMonitoring>

(🖫 Tab. 01-01-02, 05a).

11.4 Protocol Deviations

Protocol deviations were classified as “severe”, “major“ or “minor”, with severe deviations causing the exclusion from both, ITT- and PP-population, major deviations resulting in an exclusion from the PP-population only, and minor deviations not leading to an exclusion from any data set.

The following table shows major and severe protocol deviations in each treatment group.

Table 6 : Protocol deviations by severity

	C_MaxPvRate							
	Major		Minor		None		All	
	N	PctN	N	PctN	N	PctN	N	PctN
Contract								
ASTELLAS	11	39.29	12	42.86	5	17.86	28	100.00
CHIESI	4	57.14	3	42.86	.	.	7	100.00
All	15	42.86	15	42.86	5	14.29	35	100.00

(🖫 Tab. 01-01-10)

Table 7: Protocol deviations by treatment arm

		Treatment Arm					
		IM<ImmuneMonitoring>		UC<UnguidedControl>		All	
		N	PctN	N	PctN	N	PctN
Rating	PV class						
Minor	IM	1	1.02	.	.	1	1.02
	DNA	10	10.20	6	6.12	16	16.33
	HLA	5	5.10	6	6.12	11	11.22
	IMO	10	10.20	.	.	10	10.20
	INF	5	5.10	7	7.14	12	12.24
	TRT	5	5.10	6	6.12	11	11.22
	VIS	7	7.14	9	9.18	16	16.33
	All	43	43.88	34	34.69	77	78.57
Major	PV class						
	HLA	2	2.04	.	.	2	2.04
	IMO	1	1.02	5	5.10	6	6.12
	INF	3	3.06	.	.	3	3.06
	VIS	7	7.14	3	3.06	10	10.20
	All	13	13.27	8	8.16	21	21.43
All		56	57.14	42	42.86	98	100.00

(🖫 Tab. 01-01-12)

Table 8: List of major protocol violations

Patient	Site-Id	Pat-ID	Description	Occurrence	Rating	ITT	PP	SAF
4	1-Großhadern	4	Immunmonitoring results were available prior to end of study.@IMO	V5-V8	Major	Yes	No	Yes
6	1-Großhadern	6	Results of Immune monitoring were received during the study phase for this UC patient. @IMO	V5, V7	Major	Yes	No	Yes
10	1-Großhadern	10	V8 much delayed (d 420) @VIS	V8	Major	Yes	No	Yes
14	1-Großhadern	14	Early reporting of immunmonitoring results in UC arm. @IMO	V5	Major	Yes	No	Yes
14	1-Großhadern	14	Visit 6 too early (d63) and visit 8 too late (d 414) @VIS	V6, V8	Major	Yes	No	Yes
17	1-Großhadern	17	Visit 7 delayed to d220 and Visit 8 was 166 days too late @VIS	V7, V8	Major	Yes	No	Yes
18	1-Großhadern	18	Erraneous Immunmonitoring in UC Arm @IMO	V5	Major	Yes	No	Yes
20	1-Großhadern	20	Visit 8 delayed (d421) @VIS	V8	Major	Yes	No	Yes
21	1-Großhadern	21	Visit 5 (d58) and visit 8 (d433) delayed @VIS	V5, V8	Major	Yes	No	Yes
21	1-Großhadern	21	Initial HLA analysis sample taken after 2 months @HLA	V1	Major	Yes	No	Yes
24	1-Großhadern	24	V8 was done 76 days early @VIS	V8	Major	Yes	No	Yes
25	1-Großhadern	25	Visit 8 too early (d303) @VIS	V8	Major	Yes	No	Yes
28	1-Großhadern	28	Reporting of HLA assessment dates in the eCRF are indicative for premature communication of results @IMO	V1-V8	Major	Yes	No	Yes
28	1-Großhadern	28	Visit 8 was 127 days too late @VIS	V8	Major	Yes	No	Yes
29	1-Großhadern	29	V8 was 91 days early @VIS	V8	Major	Yes	No	Yes
30	1-Großhadern	30	ELISPOT not done at M6 and M12 @INF	V7, V8	Major	Yes	No	Yes
30	1-Großhadern	30	No Immune Monitoring at visit 7 @IMO	V7	Major	Yes	No	Yes
30	1-Großhadern	30	V8 was 48 days too late @VIS	V8	Major	Yes	No	Yes
30	1-Großhadern	30	No HLA analysis at visit 7. @HLA	V7	Major	Yes	No	Yes
31	1-Großhadern	31	ELISPOT not done at M6 @INF	V7	Major	Yes	No	Yes
35	1-Großhadern	35	ELISOT visit 6 not done. @INF	V6	Major	Yes	No	Yes

(🖫 Tab. 01-01-14)

11.4.1 Deviation from randomized treatment

Deviation of randomized treatment was observed in 11 patients (9 under Astellas- and 2 under Chiesi-contract)

Table 9: Deviations from the randomized treatment

Patient	Contract	Discontinuation of study treatment	Induction	Last Tacrolimus	Initial Tacrolimus	Tacrolimus changed count	Treatment Arm
15	ASTELLAS	No	Envarsus	Envarsus (ENV)	Envarsus (ENV)	0	UC<UnguidedControl>
16	ASTELLAS	No	Envarsus	Advagraf (ADV)	Envarsus (ENV)	2	IM<ImmuneMonitoring>
17	ASTELLAS	No	Envarsus	Envarsus (ENV)	Envarsus (ENV)	0	IM<ImmuneMonitoring>

Patient	Contract	Discontinuation of study treatment	Induction	Last Tacrolimus	Initial Tacrolimus	Tacrolimus changed count	Treatment Arm
18	ASTELLAS	No	Envarsus	Prograf	Envarsus (ENV)	7	UC<UnguidedControl>
20	ASTELLAS	Yes	Advagraf	Advagraf (ADV)	Advagraf (ADV)	4	IM<ImmuneMonitoring>
25	ASTELLAS	No	Prograf	Prograf	Prograf	0	UC<UnguidedControl>
26	ASTELLAS	No	Envarsus	Envarsus (ENV)	Envarsus (ENV)	0	IM<ImmuneMonitoring>
27	ASTELLAS	No	Envarsus	Envarsus (ENV)	Envarsus (ENV)	0	UC<UnguidedControl>
28	ASTELLAS	No	Envarsus	Envarsus (ENV)	Envarsus (ENV)	0	UC<UnguidedControl>
32	CHIESI	No	Advagraf	Envarsus (ENV)	Envarsus (ENV)	0	UC<UnguidedControl>
35	CHIESI	No	Advagraf	Envarsus (ENV)	Advagraf (ADV)	6	IM<ImmuneMonitoring>

(🖫 Tab. 01-01-06a)

12 EFFICACY EVALUATION

12.1 Data Sets Analysed

All data were analysed, except data of patients who had withdrawn consent.

In principle, the **Safety population** should include all patients who had taken at least one dose of the study medication. Yet, patients not treated, not treated for certain or patients with no observation after first intake of study medication were excluded from the safety evaluation. Excluding patients with no observation after the first intake from the safety population serves the purpose of consumer protection, as their exclusion leads to higher percentages of adverse events.

The **ITT population** (for first line analysis of efficacy) (ITT, full analysis set) includes all patients who had taken at least one dose of the study medication and who had had at least one observation on medication and who did not show severe protocol deviations (for details about individual protocol deviations see section 11.4).

Patients without follow-up contact with the investigator will be considered treatment failures and their initial values will be carried forward for the primary analysis.

The **PP population** includes all patients who did not show major or severe protocol deviations (for details about individual protocol deviations see section 11.4).

The per protocol population was defined to include the intent-to treat population excluding patients

- with missing and/or inadequate measurement of the primary endpoint, or
- who took less than 80% of the anticipated study medication, or more than 120 %
- with major violation of inclusion-/exclusion criteria, or
- who have other major or severe protocol violations

All included 35 patients are evaluable in the ITT population and the safety population (SAF), 28 within the contract with Astellas and 7 within the contract with Chiesi (Table 10). In the ITT population 21

patients were treated with immune monitoring (IM) and 14 were treated as unguided controls (Table 11).

Overall, 19 patients are evaluable as per protocol, 16 within the contract with Astellas and 3 within the contract with Chiesi (Table 10). 11 patients in the PP population were treated in the IM group and 8 in the UC group (Table 11).

The numbers of ITT and PP evaluable patients within the contracts and the treatment groups are shown in Table 12.

Table 10: Analysis populations by contract

	ITT		PP				SAF			
	Yes		No		Yes		Yes		All	
	N	PctN	N	PctN	N	PctN	N	PctN	N	PctN
Contract										
ASTELLAS	28	80.00	12	75.00	16	84.21	28	80.00	28	80.00
CHIESI	7	20.00	4	25.00	3	15.79	7	20.00	7	20.00
All	35	100.00	16	100.00	19	100.00	35	100.00	35	100.00

(🖫 Tab. 01-01-03)

Table 11 : Analysis populations by treatment

	ITT		PP				SAF			
	Yes		No		Yes		Yes		All	
	N	PctN	N	PctN	N	PctN	N	PctN	N	PctN
Treatment Arm										
IM<ImmuneMonitoring>	21	60.00	10	62.50	11	57.89	21	60.00	21	60.00
UC<UnguidedControl>	14	40.00	6	37.50	8	42.11	14	40.00	14	40.00
All	35	100.00	16	100.00	19	100.00	35	100.00	35	100.00

(🖫 Tab. 01-01-04)

Table 12: Analysis populations by contract and treatment

		ITT		PP				SAF			
		Yes		No		Yes		Yes		All	
		N	PctN	N	PctN	N	PctN	N	PctN	N	PctN
Contract	Treatment Arm										
ASTELLAS	IM<ImmuneMonitoring>	16	45.71	6	37.50	10	52.63	16	45.71	16	45.71
	UC<UnguidedControl>	12	34.29	6	37.50	6	31.58	12	34.29	12	34.29
CHIESI	IM<ImmuneMonitoring>	5	14.29	4	25.00	1	5.26	5	14.29	5	14.29
	UC<UnguidedControl>	2	5.71	.	.	2	10.53	2	5.71	2	5.71
All		35	100.00	16	100.00	19	100.00	35	100.00	35	100.00

(🖫 Tab. 01-01-04a)

The following tables shows exclusion from the PP population by classified protocol violations including two patients withdrawn from the randomized treatment (Pat. 01-001 and 01-020, both from the IM group (Table 14)).

Table 13: Exclusions from PP - classified

	Contract					
	ASTELLAS		CHIESI		All	
	N	PctN	N	PctN	N	PctN
Classes						
IMO:	3	25.00	.	.	3	18.75
IMO:VIS:	2	16.67	.	.	2	12.50
INF:	.	.	2	50.00	2	12.50
INF:IMO:VIS:HLA:	.	.	1	25.00	1	6.25
VIS:	4	33.33	1	25.00	5	31.25
VIS:HLA:	1	8.33	.	.	1	6.25
VIS:WDR:	1	8.33	.	.	1	6.25
WDR:	1	8.33	.	.	1	6.25
All	12	100.00	4	100.00	16	100.00

(🖫 Tab. 01-01-17)

Table 14: List of exclusion from PP

Site-Id	Pat-ID	Classes	Descriptions	Contract	Treatment
1	1	WDR:	Switch to Advagraf/Everolimus @WDR; papilläres Adenom der Spenderniere:	ASTELLAS	IM<ImmuneMonitoring>
1	4	IMO:	Immunmonitoring results were available prior to end of study.@IMO;:	ASTELLAS	UC<UnguidedControl>
1	6	IMO:	Results of Immune monitoring were received during the study phase for this UC patient. @IMO;:	ASTELLAS	UC<UnguidedControl>
1	10	VIS:	V8 much delayed (d 420) @VIS;:	ASTELLAS	IM<ImmuneMonitoring>
1	14	IMO:VIS:	Early reporting of immunmonitoring results in UC arm. @IMO;:Visit 6 too early (d63) and visit 8 too late (d 414) @VIS;:	ASTELLAS	UC<UnguidedControl>
1	17	VIS:	Visit 7 delayed to d220 and Visit 8 was 166 days too late @VIS;:	ASTELLAS	IM<ImmuneMonitoring>
1	18	IMO:	Erraneous Immunmonitoring in UC Arm @IMO;:	ASTELLAS	UC<UnguidedControl>
1	20	VIS:WDR:	Visit 8 delayed (d421) @VIS; Banff 3 Umstellung auf Certican+Prograf:Multiple switches between Advagraf and Prograf @WDR; Banff 3 Umstellung auf Certican+Prograf:	ASTELLAS	IM<ImmuneMonitoring>
1	21	VIS:HLA:	Visit 5 (d58) and visit 8 (d433) delayed @VIS;:Initial HLA analysis sample taken after 2 months @HLA;:	ASTELLAS	IM<ImmuneMonitoring>
1	24	VIS:	V8 was done 76 days early @VIS;:	ASTELLAS	IM<ImmuneMonitoring>
1	25	VIS:	Visit 8 too early (d303) @VIS;:	ASTELLAS	UC<UnguidedControl>
1	28	IMO:VIS:	Reporting of HLA assessment dates in the eCRF are indicative for premature communication of results @IMO;:Visit 8 was 127 days too late @VIS;:	ASTELLAS	UC<UnguidedControl>

Site-Id	Pat-ID	Classes	Descriptions	Contract	Treatment
1	29	VIS:	V8 was 91 days early @VIS;:	CHIESI	IM<ImmuneMonitoring>
1	30	INF:IMO:VIS:HLA:	ELISPOT not done at M6 and M12 @INF;:No Immune Monitoring at visit 7 @IMO;:V8 was 48 days too late @VIS;:No HLA analysis at visit 7. @HLA;:	CHIESI	IM<ImmuneMonitoring>
1	31	INF:	ELISPOT not done at M6 @INF;:	CHIESI	IM<ImmuneMonitoring>
1	35	INF:	ELISOT visit 6 not done. @INF;:	CHIESI	IM<ImmuneMonitoring>

(🖫 Tab. 01-01-18)

12.2 Demographic and Other Baseline Characteristics

12.2.1 Demographic and Anamnestic Criteria

Patients (recipients) were 23% female with a median age of 34 years (range: 19-63 years) (Table 15). Donors were 54% female with a median age of 56 years (range: 43-70) (Table 16). Demographic and anamnestic data are well balanced between treatment groups.

Table 15: Summary of recipient demographics and anamnestic data

			Treatment Arm		
			IM<ImmuneMon.	UC<UnguidedC.	Total
		Statistic			
Sex	Female	N(%)	6 (28.6)	2 (14.3)	8 (22.9)
	Male	N(%)	15 (71.4)	12 (85.7)	27 (77.1)
		P			0.4307
Ethnicity	Asian	N(%)	1 (4.8)		1 (2.9)
	Caucasian	N(%)	20 (95.2)	14 (100.0)	34 (97.1)
		P			1.0000
Cause of end stage renal fail...	Diabetes mellitus	N(%)	1 (4.8)		1 (2.9)
	Glomerulonephritis	N(%)	5 (23.8)	2 (14.3)	7 (20.0)
	Hypertension	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
	Other	N(%)	13 (61.9)	9 (64.3)	22 (62.9)
	Polycystic kidney disease	N(%)	1 (4.8)	2 (14.3)	3 (8.6)
		P			0.7307
Height (cm)		N	21	14	35
		MEAN	174.14	175.79	174.80
		STD	7.23	9.97	8.33
		MIN	163.00	157.00	157.00
		Q1	169.00	170.00	169.00
		MEDIAN	175.00	175.00	175.00

			Treatment Arm		
			IM<ImmuneMon.	UC<UnguidedC.	Total
		Statistic			
		Q3	178.00	185.00	180.00
		MAX	190.00	191.00	191.00
		P			0.6249
Weight (kg)		N	21	14	35
		MEAN	73.33	76.46	74.58
		STD	13.34	15.78	14.22
		MIN	46.00	50.00	46.00
		Q1	64.90	68.00	64.90
		MEDIAN	74.20	75.50	75.00
		Q3	82.00	85.00	84.00
		MAX	95.00	113.00	113.00
		P			0.6372
BMI [kf/m^2]		N	21	14	35
		MEAN	24.11	24.57	24.29
		STD	3.89	3.56	3.72
		MIN	17.10	20.08	17.10
		Q1	21.45	21.60	21.45
		MEDIAN	24.21	24.35	24.21
		Q3	27.61	28.41	27.70
		MAX	31.16	30.98	31.16
		P			0.7747
BMI [kf/m^2]	Normal range	N(%)	11 (52.4)	10 (71.4)	21 (60.0)
	Obese	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
	Overweight	N(%)	7 (33.3)	3 (21.4)	10 (28.6)
	Underweight	N(%)	2 (9.5)		2 (5.7)
		P			0.5047
Age at Inclusion		N	21	14	35
		MEAN	36.57	39.64	37.80
		STD	13.17	13.82	13.32
		MIN	19.00	21.00	19.00
		Q1	27.00	29.00	27.00
		MEDIAN	33.00	37.00	34.00
		Q3	46.00	50.00	49.00
		MAX	63.00	62.00	63.00
		P			0.3992
Age at Inclusion	18-64	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
Dialysis prior to transplantation	No	N(%)	10 (47.6)	3 (21.4)	13 (37.1)
	Yes	N(%)	11 (52.4)	11 (78.6)	22 (62.9)
		P			0.1621
Blood Type	A	N(%)	10 (47.6)	5 (35.7)	15 (42.9)
	AB	N(%)		1 (7.1)	1 (2.9)

			Treatment Arm		
			IM<ImmuneMon.	UC<UnguidedC.	Total
		Statistic			
	B	N(%)	2 (9.5)	3 (21.4)	5 (14.3)
	O	N(%)	9 (42.9)	5 (35.7)	14 (40.0)
		P			0.4371
CMV status	neg.	N(%)	10 (47.6)	10 (71.4)	20 (57.1)
	pos.	N(%)	11 (52.4)	4 (28.6)	15 (42.9)
		P			0.2958
HBsAG or HCV positive?	No	N(%)	20 (95.2)	14 (100.0)	34 (97.1)
	Yes	N(%)	1 (4.8)		1 (2.9)
		P			1.0000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 02-01-04-01)

Table 16: Summary of donor demographics and anamnestic data

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
Sex	Female	N(%)	14 (66.7)	5 (35.7)	19 (54.3)
	Male	N(%)	7 (33.3)	9 (64.3)	16 (45.7)
		P			0.0937
Anatomic Position	Left	N(%)	10 (47.6)	8 (57.1)	18 (51.4)
	Right	N(%)	11 (52.4)	6 (42.9)	17 (48.6)
		P			0.7332
Blood Type	A	N(%)	7 (33.3)	6 (42.9)	13 (37.1)
	AB	N(%)		1 (7.1)	1 (2.9)
	B	N(%)		1 (7.1)	1 (2.9)
	O	N(%)	14 (66.7)	6 (42.9)	20 (57.1)
		P			0.2573
CMV status	neg.	N(%)	13 (61.9)	6 (42.9)	19 (54.3)
	pos.	N(%)	8 (38.1)	8 (57.1)	16 (45.7)
		P			0.3167
Donor Age		N	21	14	35
		MEAN	55.14	56.86	55.83
		STD	6.41	6.70	6.48
		MIN	43.00	45.00	43.00
		Q1	50.00	50.00	50.00
		MEDIAN	55.00	59.50	56.00
		Q3	59.00	61.00	60.00
		MAX	70.00	68.00	70.00

			Treatment Arm IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
		P			0.3712
Donor Age	18-64	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
	65-84	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
		P			1.0000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 02-01-04-02)

12.2.2 Baseline Data

No significant differences between treatment groups were found in baseline data (Table 17).

Table 17: Baseline Data

		Treatment Arm IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
Cold ischemia time (h)	N	21	14	35
	MEAN	2.01	2.50	2.21
	STD	0.99	1.08	1.04
	MIN	1.00	1.00	1.00
	Q1	1.00	1.00	1.00
	MEDIAN	2.00	3.00	2.40
	Q3	3.00	3.00	3.00
	MAX	4.00	4.00	4.00
	P			0.2001
PRA (%)	N	21	14	35
	MEAN	0.00	0.00	0.00
	STD	0.00	0.00	0.00
	MIN	0.00	0.00	0.00
	Q1	0.00	0.00	0.00
	MEDIAN	0.00	0.00	0.00
	Q3	0.00	0.00	0.00
	MAX	0.00	0.00	0.00
	P			1.0000
Urine [ml/24h]	N	21	14	35
	MEAN	12827.1	12110.7	12540.6
	STD	7850.98	3041.33	6318.31
	MIN	1750.00	8200.00	1750.00
	Q1	8400.00	10550.0	9100.00

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
		MEDIAN	11450.0	11450.0	11450.0
		Q3	15000.0	12800.0	15000.0
		MAX	34300.0	19200.0	34300.0
		P			0.9731
Creatinine [mg/dl]		N	20	14	34
		MEAN	5.38	5.67	5.50
		STD	2.29	2.84	2.49
		MIN	2.30	2.20	2.20
		Q1	3.05	3.20	3.20
		MEDIAN	5.30	4.95	5.30
		Q3	6.60	7.80	7.70
		MAX	9.90	10.90	10.90
		P			0.9442
Time to diuresis	Delayed	N(%)	1 (4.8)		1 (2.9)
	Immediate	N(%)	20 (95.2)	14 (100.0)	34 (97.1)
		P			1.0000
Induction	Advagraf	N(%)	13 (61.9)	8 (57.1)	21 (60.0)
	Envarsus	N(%)	8 (38.1)	5 (35.7)	13 (37.1)
	Prograf	N(%)		1 (7.1)	1 (2.9)
		P			0.4620
ADV Dose		N	13	8	21
		MEAN	13.35	14.75	13.88
		STD	2.36	5.26	3.67
		MIN	9.00	4.00	4.00
		Q1	12.00	14.00	12.00
		MEDIAN	14.00	15.00	15.00
		Q3	15.00	16.50	15.50
		MAX	16.00	23.00	23.00
		P			0.2258
ENV Dose		N	8	5	13
		MEAN	8.63	9.80	9.08
		STD	4.44	5.36	4.63
		MIN	4.00	4.00	4.00
		Q1	5.00	5.00	5.00
		MEDIAN	7.50	11.00	9.00
		Q3	12.50	12.00	12.00
		MAX	15.00	17.00	17.00
		P			0.7678
PRO Dose		N	0	1	1
		MEAN	.	5.00	5.00
		STD	.	.	.

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
		MIN	.	5.00	5.00
		Q1	.	5.00	5.00
		MEDIAN	.	5.00	5.00
		Q3	.	5.00	5.00
		MAX	.	5.00	5.00
CMV Combination	P+D+	N(%)	6 (28.6)	3 (21.4)	9 (25.7)
	P+D-	N(%)	5 (23.8)	1 (7.1)	6 (17.1)
	P-D+	N(%)	2 (9.5)	5 (35.7)	7 (20.0)
	P-D-	N(%)	8 (38.1)	5 (35.7)	13 (37.1)
		P			0.2194

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 02-01-04-03)

12.2.3 Baseline Characteristics of Efficacy Criteria

For one patient a complication during surgery has been reported and later complications were reported in 22 patients with no significant differences between treatment arms. All complications were recorded as adverse events in detail. No dialysis has been reported in study patients after renal transplantation (Table 18).

The patients stayed median 12 days in hospital (range: 8-59 days) with no significant differences between treatment arms (Figure 3).

Table 18: Surgery and hospital stay

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
OP Complications	No	N(%)	20 (95.2)	14 (100.0)	34 (97.1)
	Yes	N(%)	1 (4.8)		1 (2.9)
		P			1.0000
Had dialyses	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
Had complications	No	N(%)	10 (47.6)	3 (21.4)	13 (37.1)
	Yes	N(%)	11 (52.4)	11 (78.6)	22 (62.9)
		P			0.1621
Number of complications		N	21	14	35
		MEAN	1.19	1.50	1.31
		STD	1.44	1.22	1.35
		MIN	0.00	0.00	0.00
		Q1	0.00	1.00	0.00

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
	MEDIAN	1.00	1.00	1.00
	Q3	2.00	2.00	2.00
	MAX	5.00	4.00	5.00
	P			0.3449
Day of first discharge	N	21	14	35
	MEAN	15.29	15.71	15.46
	STD	11.62	6.04	9.66
	MIN	8.00	8.00	8.00
	Q1	9.00	12.00	9.00
	MEDIAN	12.00	14.50	12.00
	Q3	13.00	19.00	19.00
	MAX	59.00	28.00	59.00
	P			0.1902

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 02-02-04-01)

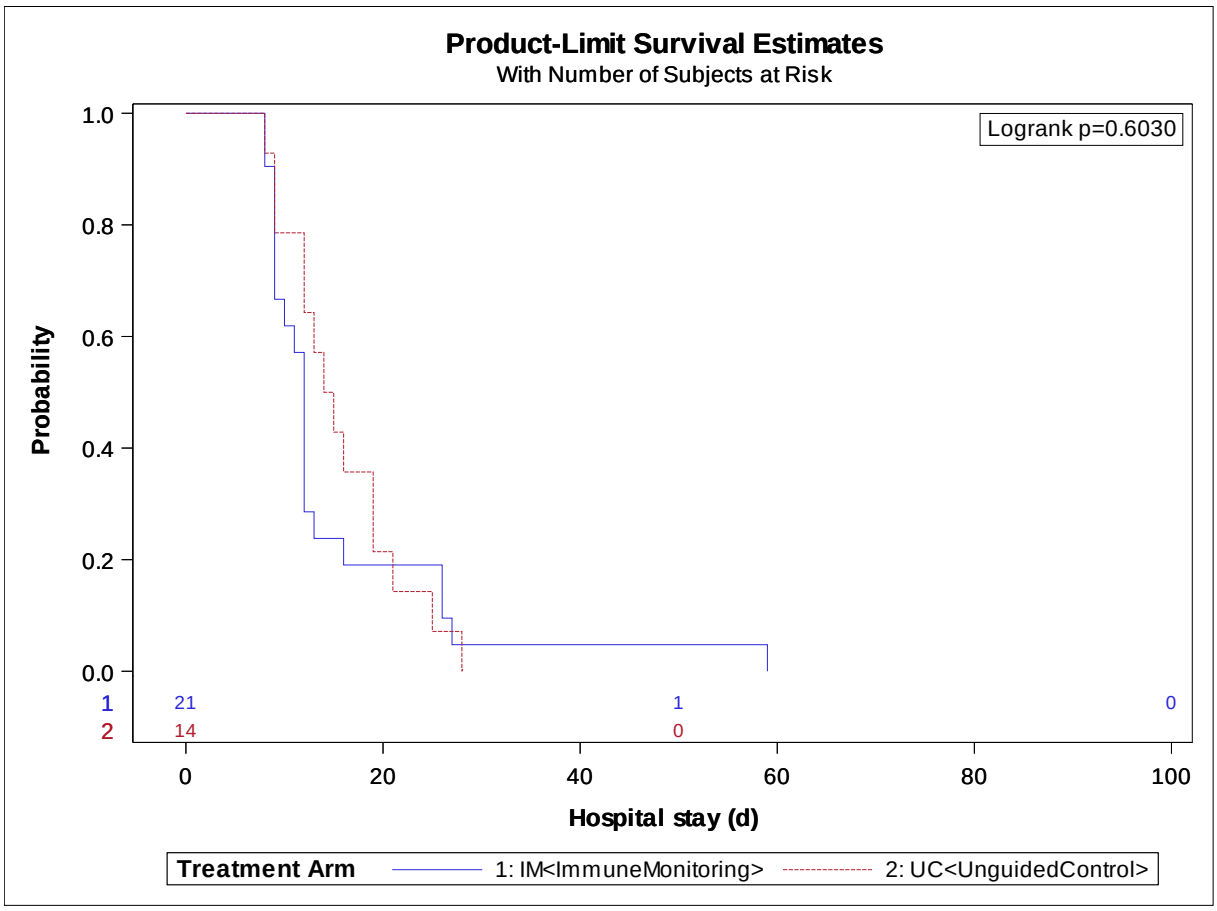

Figure 3: Duration of hospitalization

(🖫 Tab. 02-02-04-03)

12.3 Measurements of the Treatment Compliance

12.4 Immune Monitoring

Immune monitoring results are available in both treatment arms, but they were differently handled during the study. While in the immune monitoring (IM) arm the results were directly communicated from the laboratory to the investigator who adjusted further dosing in response to the results, in the unguided control group (UC) the results were kept hidden from the investigator who followed the standard dosing scheme for the patient. In the control group the results were delivered after the patient has completed the study.

At study entry no donor specific HLA antibodies were present, but 60% of the patients (57% in the IM and 64% in the UC group) were already INFγ positive (no difference between treatment arm p=0.4566) (Table 19).

At the end of study visit (visit 8) donor specific HLA antibodies were found in 3 UC patients (21.4%) and 1 IM patient (4.8%) but the difference is not significant (p=0.2830). INFγ positivity was found in 86% of the UC patients and 62% of the IM patients (p=1.0000). Circulating donor derived DNA was not analysed for any of the patients at the end of the study (Table 20).

Table 19: Immune monitoring results at study entry (V1)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
HLA antibodies detected?	No	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
	Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
		P			1.0000
Donor specific HLA antibodies...	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
Non donor specific HLA Antibodies	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
INFy positive?	.	N(%)		2 (14.3)	2 (5.7)
	No	N(%)	9 (42.9)	3 (21.4)	12 (34.3)
	Yes	N(%)	12 (57.1)	9 (64.3)	21 (60.0)
		P			0.4566
Value [spots/3x10 responder...		N	21	12	33
		MEAN	54.24	59.92	56.30
		STD	52.74	38.17	47.40
		MIN	0.00	0.00	0.00
		Q1	11.00	27.00	17.00
		MEDIAN	39.00	65.50	47.00
		Q3	77.00	91.00	80.00
		MAX	177.00	119.00	177.00

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
	P			0.5122

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-02-01-01b)

Table 20: Immune monitoring results at the end of the study (V8)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
HLA antibodies detected?	.	N(%)	1 (4.8)		1 (2.9)
	No	N(%)	19 (90.5)	11 (78.6)	30 (85.7)
	Yes	N(%)	1 (4.8)	3 (21.4)	4 (11.4)
		P			0.2830
Donor specific HLA antibodies...	.	N(%)	1 (4.8)		1 (2.9)
	No	N(%)	19 (90.5)	11 (78.6)	30 (85.7)
	Yes	N(%)	1 (4.8)	3 (21.4)	4 (11.4)
		P			0.2830
Non donor specific HLA Antibodies	.	N(%)	1 (4.8)		1 (2.9)
	No	N(%)	19 (90.5)	13 (92.9)	32 (91.4)
	Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
		P			1.0000
INFy positive?	.	N(%)	6 (28.6)		6 (17.1)
	No	N(%)	2 (9.5)	2 (14.3)	4 (11.4)
	Yes	N(%)	13 (61.9)	12 (85.7)	25 (71.4)
		P			1.0000
Value [spots/3x10 responder...		N	15	14	29
		MEAN	82.73	76.79	79.86
		STD	70.94	46.84	59.53
		MIN	5.00	8.00	5.00
		Q1	40.00	34.00	40.00
		MEDIAN	68.00	75.00	70.00
		Q3	119.00	107.00	115.00
		MAX	283.00	170.00	283.00
		P			0.9826
Circulating donor derived DNA...	.	N(%)	11 (52.4)	6 (42.9)	17 (48.6)
	No	N(%)	10 (47.6)	8 (57.1)	18 (51.4)
BPAR/visit	No	N(%)	20 (95.2)	14 (100.0)	34 (97.1)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
	Yes	N(%)	1 (4.8)		1 (2.9)
		P			1.0000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-02-01-02b)

Donor-specific HLA antibodies as well as INFγ can be positive at one visit and negative at the next visit. Therefore, the cumulative incidence should be regarded as more meaningful. As shown in Table 21 there are numerically more HLA antibodies (50% vs. 19%) and more donor specific HLA antibodies (27% vs. 5%) in the UC group than in the IM group, but the difference is not significant (p=0.0725 and p=0.1336). 91% oft he patients in the IM group were INFγ positive compared to 93% in the UC group. As a consequence, 91% of the patients in the IM group had at least at one time point a positive immunological result during the conduct of the study. This is reduced to 81% INFγ positive patients in the IM arm and 86% of the patients with a positive immune monitoring result during the study when the baseline values are excluded (Table 22). The cumulative results until each visit are shown in Table 23

Table 21: Cumulative immune monitoring result during the study.

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
Has HLA Ab	No	N(%)	17 (81.0)	7 (50.0)	24 (68.6)
	Yes	N(%)	4 (19.0)	7 (50.0)	11 (31.4)
		P			0.0725
Has DSA	No	N(%)	20 (95.2)	10 (71.4)	30 (85.7)
	Yes	N(%)	1 (4.8)	4 (28.6)	5 (14.3)
		P			0.1336
Has nDSA	No	N(%)	19 (90.5)	12 (85.7)	31 (88.6)
	Yes	N(%)	2 (9.5)	2 (14.3)	4 (11.4)
		P			1.0000
Has INFy	No	N(%)	2 (9.5)	1 (7.1)	3 (8.6)
	Yes	N(%)	19 (90.5)	13 (92.9)	32 (91.4)
		P			1.0000
Has DDNA	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
	No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
Has DSA or INFy	No	N(%)	2 (9.5)		2 (5.7)
	Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
		P			0.5059
Has BPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
		P			1.0000
Has DSA/INFy/BPAR	No	N(%)	2 (9.5)		2 (5.7)
	Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
		P			0.5059

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-02-01-03b)

Table 22: Cumulative immune monitoring result after baseline

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
Has post-BL HLA Ab	No	N(%)	18 (85.7)	8 (57.1)	26 (74.3)
	Yes	N(%)	3 (14.3)	6 (42.9)	9 (25.7)
		P			0.1122
Has post-BL DSA	No	N(%)	20 (95.2)	10 (71.4)	30 (85.7)
	Yes	N(%)	1 (4.8)	4 (28.6)	5 (14.3)
		P			0.1336
Has post-BL nDSA	No	N(%)	19 (90.5)	12 (85.7)	31 (88.6)
	Yes	N(%)	2 (9.5)	2 (14.3)	4 (11.4)
		P			1.0000
Has post-BL INFy	No	N(%)	4 (19.0)	1 (7.1)	5 (14.3)
	Yes	N(%)	17 (81.0)	13 (92.9)	30 (85.7)
		P			0.6272
Has post-BL DDNA	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
	No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
Has post-BL DSA or INFy	No	N(%)	4 (19.0)		4 (11.4)
	Yes	N(%)	17 (81.0)	14 (100.0)	31 (88.6)
		P			0.1334
Has BPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
Has post-BL DSA/INFy/BPAR	No	N(%)	3 (14.3)		3 (8.6)
	Yes	N(%)	18 (85.7)	14 (100.0)	32 (91.4)
		P			0.2588

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-02-01-04b)

Table 23: Immune monitoring results by visits

				Treatment Arm		
				IM<ImmuneMon	UC<UnguidedC	Total
	Visit		Statistic			
Has HLA Ab	1	No	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
		Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
			P			1.0000
	5	No	N(%)	18 (85.7)	11 (78.6)	29 (82.9)
		Yes	N(%)	3 (14.3)	3 (21.4)	6 (17.1)
			P			0.6645
	6	No	N(%)	18 (85.7)	9 (64.3)	27 (77.1)
		Yes	N(%)	3 (14.3)	5 (35.7)	8 (22.9)
			P			0.2209
	7	No	N(%)	18 (85.7)	8 (57.1)	26 (74.3)
		Yes	N(%)	3 (14.3)	6 (42.9)	9 (25.7)
			P			0.1122
	8	No	N(%)	17 (81.0)	7 (50.0)	24 (68.6)
		Yes	N(%)	4 (19.0)	7 (50.0)	11 (31.4)
			P			0.0725
Has DSA	1	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
	5	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
	6	No	N(%)	21 (100.0)	12 (85.7)	33 (94.3)
		Yes	N(%)		2 (14.3)	2 (5.7)
			P			0.1529
	7	No	N(%)	21 (100.0)	11 (78.6)	32 (91.4)
		Yes	N(%)		3 (21.4)	3 (8.6)
			P			0.0556
	8	No	N(%)	20 (95.2)	10 (71.4)	30 (85.7)
		Yes	N(%)	1 (4.8)	4 (28.6)	5 (14.3)
			P			0.1336
Has nDSA	1	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
	5	No	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
		Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
			P			1.0000
	6	No	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
		Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
			P			1.0000
	7	No	N(%)	20 (95.2)	13 (92.9)	33 (94.3)
		Yes	N(%)	1 (4.8)	1 (7.1)	2 (5.7)
			P			1.0000
	8	No	N(%)	19 (90.5)	12 (85.7)	31 (88.6)
		Yes	N(%)	2 (9.5)	2 (14.3)	4 (11.4)
			P			1.0000
Has INFy	1	.	N(%)		2 (14.3)	2 (5.7)

				Treatment Arm		
				IM<ImmuneMon	UC<UnguidedC	Total
	Visit		Statistic			
		No	N(%)	9 (42.9)	3 (21.4)	12 (34.3)
		Yes	N(%)	12 (57.1)	9 (64.3)	21 (60.0)
			P			0.4566
	5	No	N(%)	5 (23.8)	3 (21.4)	8 (22.9)
		Yes	N(%)	16 (76.2)	11 (78.6)	27 (77.1)
			P			1.0000
	6	No	N(%)	3 (14.3)	3 (21.4)	6 (17.1)
		Yes	N(%)	18 (85.7)	11 (78.6)	29 (82.9)
			P			0.6645
	7	No	N(%)	3 (14.3)	2 (14.3)	5 (14.3)
		Yes	N(%)	18 (85.7)	12 (85.7)	30 (85.7)
			P			1.0000
	8	No	N(%)	2 (9.5)	1 (7.1)	3 (8.6)
		Yes	N(%)	19 (90.5)	13 (92.9)	32 (91.4)
			P			1.0000
Has DDNA	1	.	N(%)	21 (100.0)	14 (100.0)	35 (100.0)
	5	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
		No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
	6	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
		No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
	7	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
		No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
	8	.	N(%)	9 (42.9)	6 (42.9)	15 (42.9)
		No	N(%)	12 (57.1)	8 (57.1)	20 (57.1)
Has DSA or INFy	1	.	N(%)		2 (14.3)	2 (5.7)
		No	N(%)	9 (42.9)	3 (21.4)	12 (34.3)
		Yes	N(%)	12 (57.1)	9 (64.3)	21 (60.0)
			P			0.4566
	5	No	N(%)	5 (23.8)	3 (21.4)	8 (22.9)
		Yes	N(%)	16 (76.2)	11 (78.6)	27 (77.1)
			P			1.0000
	6	No	N(%)	3 (14.3)	2 (14.3)	5 (14.3)
		Yes	N(%)	18 (85.7)	12 (85.7)	30 (85.7)
			P			1.0000
	7	No	N(%)	3 (14.3)	1 (7.1)	4 (11.4)
		Yes	N(%)	18 (85.7)	13 (92.9)	31 (88.6)
			P			0.6350
	8	No	N(%)	2 (9.5)		2 (5.7)
		Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
			P			0.5059
Has BPAR	1	No	N(%)	21 (100.0)	14 (100.0)	35 (100.0)

				Treatment Arm		
				IM<ImmuneMon	UC<UnguidedC	Total
	Visit		Statistic			
	5	No	N(%)	15 (71.4)	9 (64.3)	24 (68.6)
		Yes	N(%)	6 (28.6)	5 (35.7)	11 (31.4)
			P			0.7210
	6	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
		Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
			P			1.0000
	7	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
		Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
			P			1.0000
	8	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
		Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
			P			1.0000
Has DSA/INFγ/BPAR	1	No	N(%)	9 (42.9)	5 (35.7)	14 (40.0)
		Yes	N(%)	12 (57.1)	9 (64.3)	21 (60.0)
			P			0.7366
	5	No	N(%)	4 (19.0)		4 (11.4)
		Yes	N(%)	17 (81.0)	14 (100.0)	31 (88.6)
			P			0.1334
	6	No	N(%)	2 (9.5)		2 (5.7)
		Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
			P			0.5059
	7	No	N(%)	2 (9.5)		2 (5.7)
		Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
			P			0.5059
	8	No	N(%)	2 (9.5)		2 (5.7)
		Yes	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
			P			0.5059

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-02-04-01b)

12.4.1 Tacrolimus Trough Levels

Considering mean tacrolimus through levels by visit there is no significant difference between immune monitoring and unguided control, with the exception of visit 8 where C0 in the IM group is 4.97±1.67 and is 6.35±1.30 ng/ml in the unguided control (p=0.0040) (Table 24 and Figure 4).

The tacrolimus trough levels recorded during the study should be seen together with the immune monitoring results. Only 3 patients were not INFγ or DSA positive or had no BPAR. All others switched back to the scheme of the unguided control at some time point during the study (Table 22).

Detailed TAC levels together with immune monitoring parameters can be found in individual figures for all patients in the appendix (🖫 Abb. 04-03-01-01,-35) showing the difficulties to keep a patient in the target trough level range.

Table 24: Tacrolimus through levels by visit

			Treatment Arm		
			IM	UC	Total
	Visit	Statistic			
C0 [ng/ml]	2	N	21	14	35
		MEAN	8.47	7.31	8.01
		STD	3.04	2.59	2.89
		MIN	4.40	2.50	2.50
		Q1	5.70	5.90	5.70
		MEDIAN	7.40	7.10	7.10
		Q3	10.70	9.10	10.30
		MAX	15.20	11.50	15.20
		P			0.4087
	3	N	21	14	35
		MEAN	9.61	10.09	9.81
		STD	4.74	3.94	4.38
		MIN	5.00	5.40	5.00
		Q1	7.40	7.20	7.20
		MEDIAN	8.80	8.55	8.80
		Q3	10.50	12.50	11.00
		MAX	28.70	18.30	28.70
		P			0.5669
	4	N	21	13	34
		MEAN	10.78	11.20	10.94
		STD	2.44	2.91	2.60
		MIN	6.90	8.30	6.90
		Q1	8.90	8.50	8.50
		MEDIAN	10.90	11.50	11.10
		Q3	13.10	12.20	12.60
		MAX	15.20	18.50	18.50
		P			0.7902
	5	N	21	14	35
		MEAN	10.88	11.84	11.26
		STD	2.17	3.49	2.76
		MIN	8.20	7.30	7.30
		Q1	8.70	8.90	8.70
		MEDIAN	10.50	11.55	10.80
		Q3	12.00	13.50	13.20
		MAX	15.10	19.10	19.10

		Treatment Arm		
		IM	UC	Total
Visit	Statistic			
	P			0.5005
6	N	21	14	35
	MEAN	8.72	8.64	8.69
	STD	3.28	1.77	2.74
	MIN	4.40	5.90	4.40
	Q1	6.00	7.30	6.60
	MEDIAN	7.70	8.35	8.00
	Q3	10.40	10.50	10.50
	MAX	15.80	11.30	15.80
	P			0.5556
7	N	21	14	35
	MEAN	7.27	7.34	7.30
	STD	2.75	2.01	2.45
	MIN	4.00	4.40	4.00
	Q1	4.70	5.40	5.20
	MEDIAN	7.20	7.15	7.20
	Q3	8.60	8.80	8.80
	MAX	14.30	11.10	14.30
	P			0.5782
8	N	21	14	35
	MEAN	4.97	6.35	5.52
	STD	1.67	1.30	1.66
	MIN	2.50	3.50	2.50
	Q1	3.80	5.60	4.10
	MEDIAN	4.90	6.45	5.50
	Q3	5.50	7.10	6.70
	MAX	9.60	8.50	9.60
	P			0.0040

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 04-03-02)

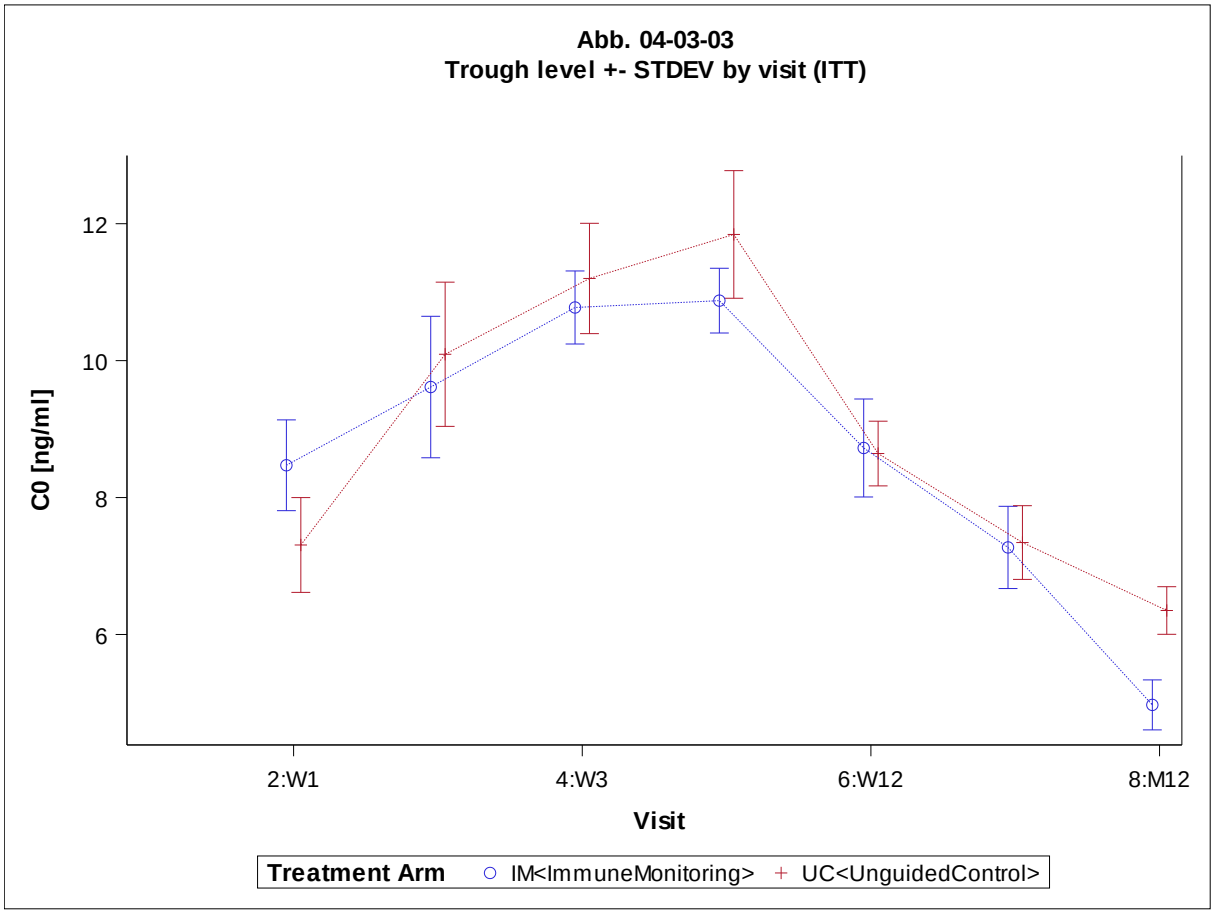

Figure 4: TAC through level by visit

(🖫 Abb. 04-03-03)

12.5 Efficacy Results and Tabulations of Individual Patient Data

Efficacy criteria were analysed in the ITT population as well as in the PP population. The primary analysis was defined as intent to treat and the per protocol analysis is considered supportive.

12.5.1 Analysis of Efficacy

12.5.1.1. Primary Criteria of Efficacy

The primary endpoint eGFR by the MDRD-4 formula does not show a significant difference between the immune monitored group and the unguided control. The Wilcoxon rank sum test pre-specified for the analysis was not significant (p=0.1524). As the median (IM: 53.85 vs. UC: 58.49) as well as the mean (IM: 52.57±16.92 vs. UC: 60.66±12.72 (mean±STD)) are smaller in the group with immune monitoring, compared to the unguided control the study hypothesis is not supported by the result of the study.

Table 25: Primary endpoint eGFR at the 12-month visit (ITT)

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
eGFR (MDRD-4) [ml/min/1.73m]	N	21	14	35
	NMISS	0	0	0
	MEAN	52.57	60.66	55.81
	STD	16.92	12.72	15.70
	LCLM	44.87	53.32	50.42
	UCLM	60.28	68.01	61.20
	MIN	14.57	43.77	14.57
	Q1	43.09	50.24	47.99
	MEDIAN	53.85	58.49	55.32
	Q3	60.43	65.95	65.95
	MAX	76.26	89.51	89.51
	P			0.1524

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-02-03-01)

While creatinine shows a highly skewed distribution the distribution of eGRF is acceptable normal (Shapiro Wilk Test p=0.2910). Therefore, a TTest would also be an acceptable analysis and with equal variances the difference between the treatment groups is not significant (p=0.1377). Taking this as sensitivity analyses supports the result of the primary analysis.

Table 26: TTest for eGFR at the 12-month analysed

Treatment	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
IM<ImmuneMonitoring>		52.5741	44.8706	60.2777	16.9236	12.9476	24.4389
UC<UnguidedControl>		60.6611	53.3164	68.0058	12.7207	9.2219	20.4935
Diff (1-2)	Pooled	-8.0869	-18.9011	2.7273	15.4054	12.4256	20.2778

(P=0.1377, with equal variances)
(🖫 Tab. 06-01-01-04)

Looking at the distribution oft he eGFR (MDRD-4) (Figure 5) it can be seen that in contrast to the unguided control group, in the immune monitored group there are patients with very bad renal function. Only two patients had an eGFR < 35 ml/min/1.37m^2 and both were in the IM group (Patient 26, 34) (Table 27). These two patients hat multiple adverse events and complications after transplantation and a bad renal function from the beginning. On the other hand, the unguided controls show a shoulder at the higher end of measured eGFR.

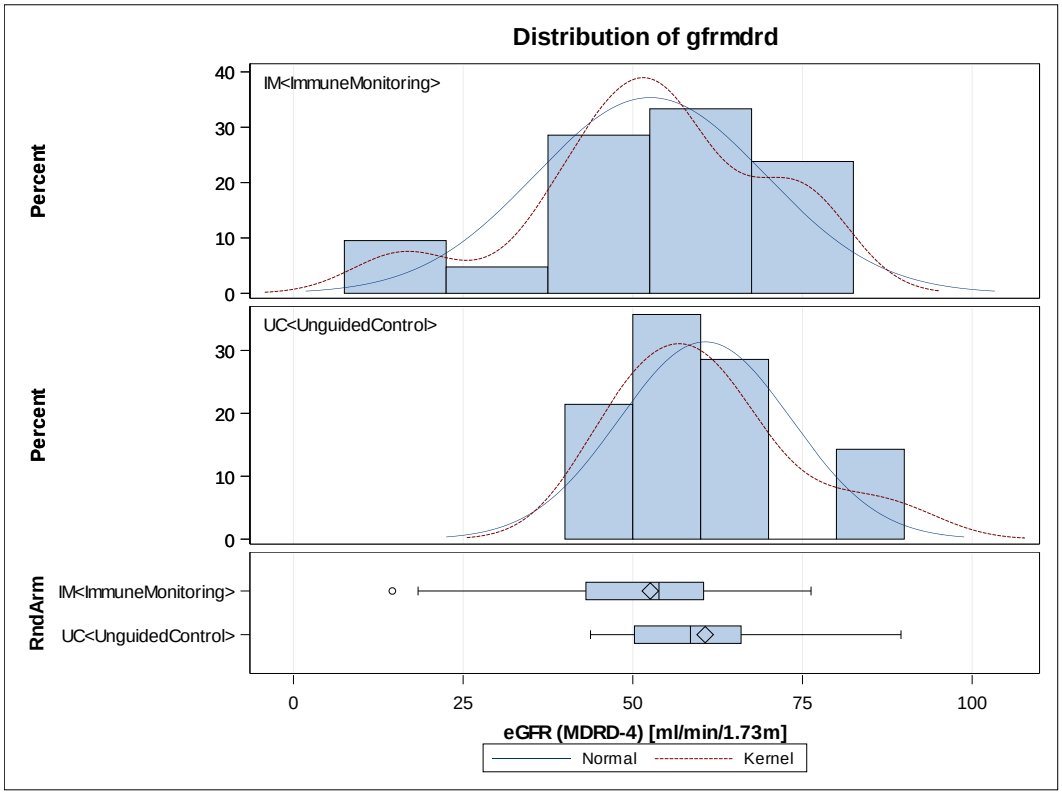

Figure 5: Distribution of eGFR (MDRD-4) at the end of study visit

Table 27: Extreme values of eGFR(MDRD-4)

Obs	eGFR(MDRD-4)	Treatment	SiteId	SubjId
1	14.5679	IM<ImmuneMonitoring>	1	34
2	18.3589	IM<ImmuneMonitoring>	1	26
3	36.5988	IM<ImmuneMonitoring>	1	20
4	41.2520	IM<ImmuneMonitoring>	1	22
5	42.8452	IM<ImmuneMonitoring>	1	12
31	75.1290	IM<ImmuneMonitoring>	1	2
32	75.2994	IM<ImmuneMonitoring>	1	8
33	76.2623	IM<ImmuneMonitoring>	1	35
34	80.4685	UC<UnguidedControl>	1	18
35	89.5149	UC<UnguidedControl>	1	25

(🖫 Tab. 06-01-01-05)

Another sensitivity analyses had the two patients with cumulated complications excluded. The result is identical with the primary analysis when the focus is on the median and only the mean is influenced by these two patients (Table 28). Overall, the result shows the same

tendency of a small numerical advantage fort he unguided control (not statistically significant; p=0.2991).

Table 28: Sensitivity analysis with extremes excluded

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	N	19	14	33
	NMISS	0	0	0
	MEAN	56.38	60.66	58.19
	STD	12.56	12.72	12.61
	LCLM	50.32	53.32	53.72
	UCLM	62.43	68.01	62.67
	MIN	36.60	43.77	36.60
	Q1	47.26	50.24	48.68
	MEDIAN	53.85	58.49	55.67
	Q3	71.63	65.95	65.95
	MAX	76.26	89.51	89.51
	P			0.2991

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-02-13-01)

Considering that the end of study is long after the scheduled 12 months in a number of patients for a further sensitivity analysis a subgroup of patients was analysed with the restriction that the last visit should not be delayed more than 30 days. This results in 27 evaluable patients also showing numerically the better renal function in the unguided control group, but the results are far from being significant. Taken as sensitivity analysis this subgroup supports the result of the primary analysis.

Table 29: eGFR at the 12-month visit < day 395

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	N	15	12	27
	NMISS	0	0	0
	MEAN	52.30	61.52	56.40
	STD	19.00	13.62	17.17
	LCLM	41.78	52.87	49.61

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
	UCLM	62.82	70.18	63.19
	MIN	14.57	43.77	14.57
	Q1	42.85	49.46	47.99
	MEDIAN	53.85	61.08	57.02
	Q3	73.37	67.91	69.86
	MAX	76.26	89.51	89.51
	P			0.2133

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-02-04-01)

12.5.1.2. Secondary Criteria of Efficacy

12.5.1.2.1 Renal Function Parameters at the End of the Study

The primary endpoint (eGFR (MDRD-4) 12 months after transplantation) for the per protocol population showed median 48 mg/ml/1.73 m2 in the IM group compared to 58 mg/ml/1.73 m2 in the UC group. The difference is statistically not significant (p=0.1731) (Table 30). The result in the PP population supports the finding for the ITT population of numerically lower eGFR in the immune monitored group compared to the unguided control group, but no significant differences can be shown.

Comparing renal function by other parameters shows the same tendency as the primary endpoint for all applied formulas (Table 31). No significant differences were detected.

Table 30: eGFR (MDRD-4) after 12 months of follow up (PP)

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	N	11	8	19
	NMISS	0	0	0
	MEAN	47.33	57.15	51.46
	STD	19.23	9.10	16.20
	LCLM	34.41	49.54	43.65
	UCLM	60.24	64.76	59.27
	MIN	14.57	43.77	14.57
	Q1	41.25	49.21	43.09
	MEDIAN	47.99	58.49	50.91
	Q3	57.28	64.08	62.20

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
	MAX	75.30	69.86	75.30
	P			0.1731

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-06-03-01)

Table 31: Continuous renal function parameters after 12 months of follow up (ITT)

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
Creatinine (mg/dl)	N	21	14	35
	MEAN	1.73	1.39	1.59
	STD	0.93	0.25	0.75
	MIN	0.90	0.80	0.80
	Q1	1.20	1.30	1.20
	MEDIAN	1.60	1.40	1.50
	Q3	1.80	1.50	1.70
	MAX	4.60	1.70	4.60
	P			0.3703
Crea-Cl.(Cockroft Gault) [ml/min/1.73m^2]	N	21	14	35
	MEAN	60.15	68.73	63.59
	STD	18.45	15.25	17.53
	MIN	17.79	44.50	17.79
	Q1	50.92	55.72	52.65
	MEDIAN	61.64	68.89	65.97
	Q3	71.50	76.28	75.07
	MAX	96.02	98.27	98.27
	P			0.1835
eGFR (Nankivell) [ml/min/1.73m^2]	N	21	14	35
	MEAN	60.64	66.59	63.02
	STD	16.01	12.04	14.66
	MIN	25.42	57.40	25.42
	Q1	51.94	58.58	57.40
	MEDIAN	59.84	62.56	61.17
	Q3	66.58	69.59	69.59
	MAX	92.47	101.67	101.67
	P			0.2888
eGFR (CKD-EPI) [ml/min/1.73m^2]	N	21	14	35

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
	Statistic			
	MEAN	54.88	63.28	58.24
	STD	18.53	15.41	17.61
	MIN	14.00	42.58	14.00
	Q1	44.68	50.04	48.84
	MEDIAN	56.56	60.53	57.78
	Q3	65.45	71.41	70.57
	MAX	82.26	98.93	98.93
	P			0.2453

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-02-03-02)

None of the binary endpoints defined for renal function is significant. The binary criteria based on creatinine rather show a difference than the ones based on the MDRD-4 formula with surprisingly 52.5% of the IM-patients having S-Cr.> 1.5 mg/dl at the end of the study compared to 21.4% in the UC group (Table 32).

Table 32: Failure rates by renal function thresholds (ITT)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
S-Cr >1.5 mg/dl	No	N(%)	10 (47.6)	11 (78.6)	21 (60.0)
	Yes	N(%)	11 (52.4)	3 (21.4)	14 (40.0)
		P			0.0885
S-Cr >2.0 mg/dl	No	N(%)	18 (85.7)	14 (100.0)	32 (91.4)
	Yes	N(%)	3 (14.3)		3 (8.6)
		P			0.2588
S-Cr CFM3 > 0.3 mg/dl	No	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
	Yes	N(%)	2 (9.5)		2 (5.7)
		P			0.5059
S-Cr CFM6 > 0.3 mg/dl	No	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
	Yes	N(%)	2 (9.5)		2 (5.7)
		P			0.5059
MDRD-4 < 50 ml/min/1.73m^2	No	N(%)	13 (61.9)	11 (78.6)	24 (68.6)
	Yes	N(%)	8 (38.1)	3 (21.4)	11 (31.4)
		P			0.4606
MDRD-4 CFM3 < -10 ml/min/1.73m^2	No	N(%)	21 (100.0)	13 (92.9)	34 (97.1)
	Yes	N(%)		1 (7.1)	1 (2.9)
		P			0.4000

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
MDRD-4 CFM6 < -10 ml/min/1.73m²	No	N(%)	21 (100.0)	13 (92.9)	34 (97.1)
	Yes	N(%)		1 (7.1)	1 (2.9)
		P			0.4000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-02-03-03)

12.5.1.2.2 Renal Function during the Study

The following tables and figures show renal function parameters during the study. An acceptable renal function can be found after week 4, but there was a continuous improvement until the last visit 12 months after transplantation. The result is comparable with all renal function parameters (Table 33 - Table 37 and Figure 6 - Figure 10).

Table 33: eGFR (MDRD-4) during the course of the study

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	1:Bas	N	21	14	35
		MEAN	8.55	8.72	8.62
		STD	2.35	3.75	2.94
		MIN	4.07	4.34	4.07
		Q1	6.81	5.79	6.72
		MEDIAN	8.75	8.93	8.82
		Q3	10.15	10.63	10.42
		MAX	13.03	18.20	18.20
		P			0.9597
	2:W1	N	21	14	35
		MEAN	33.94	31.89	33.12
		STD	21.36	15.43	18.99
		MIN	4.08	8.13	4.08
		Q1	19.02	15.05	18.29
		MEDIAN	25.96	32.01	31.21
		Q3	47.35	42.61	44.46
		MAX	75.92	56.45	75.92
		P			0.8796

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
	3:W2	N	21	14	35
		MEAN	37.85	37.79	37.82
		STD	17.96	17.93	17.68
		MIN	4.62	8.01	4.62
		Q1	29.70	30.75	29.70
		MEDIAN	38.61	39.41	38.61
		Q3	50.40	48.71	50.40
		MAX	66.01	62.79	66.01
		P			0.9597
	4:W3	N	21	13	34
		MEAN	43.03	38.73	41.38
		STD	15.81	11.93	14.42
		MIN	7.01	16.36	7.01
		Q1	34.77	34.18	34.18
		MEDIAN	44.22	38.37	42.24
		Q3	54.34	43.64	52.62
		MAX	68.01	62.79	68.01
		P			0.2719
	5:W4	N	21	14	35
		MEAN	47.40	49.07	48.07
		STD	14.14	9.04	12.23
		MIN	8.32	29.50	8.32
		Q1	39.61	42.66	41.40
		MEDIAN	47.26	49.46	48.31
		Q3	59.71	53.73	59.67
		MAX	67.35	62.79	67.35
		P			0.6017
	6:W12	N	21	14	35
		MEAN	48.67	54.63	51.06
		STD	13.96	8.60	12.32
		MIN	13.29	42.61	13.29
		Q1	40.38	48.99	43.91
		MEDIAN	49.58	52.16	50.91
		Q3	59.71	62.79	62.79
		MAX	68.01	73.33	73.33
		P			0.2593
	7:M6	N	21	14	35
		MEAN	51.20	57.45	53.70
		STD	15.40	11.71	14.20
		MIN	18.73	37.78	18.73
		Q1	41.91	47.10	43.61

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	50.91	56.07	53.85
		Q3	59.71	69.19	65.32
		MAX	79.96	74.06	79.96
		P			0.2320
	8:M12	N	21	14	35
		MEAN	52.57	60.66	55.81
		STD	16.92	12.72	15.70
		MIN	14.57	43.77	14.57
		Q1	43.09	50.24	47.99
		MEDIAN	53.85	58.49	55.32
		Q3	60.43	65.95	65.95
		MAX	76.26	89.51	89.51
		P			0.1524

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-04-22-04)

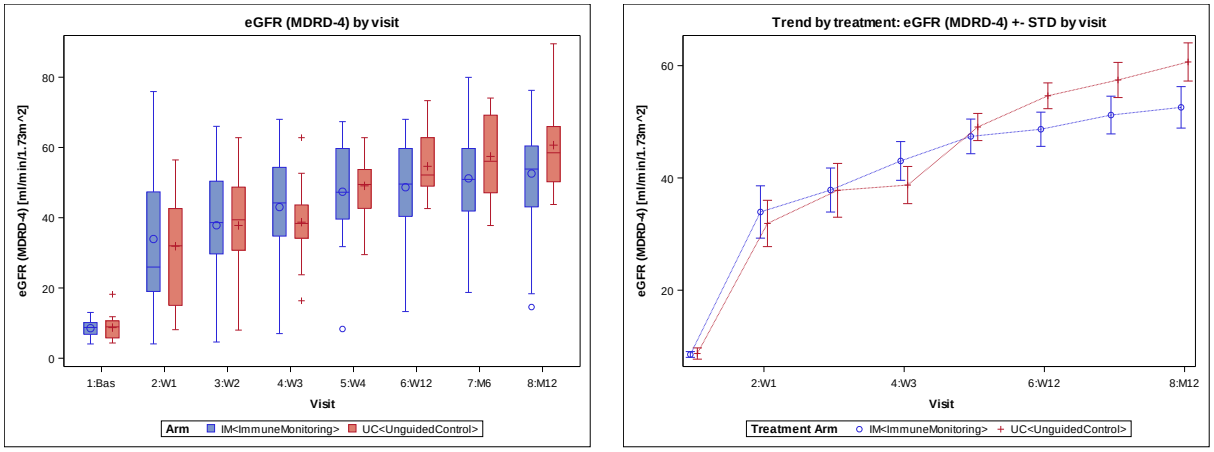

Figure 6: eGFR (MDRD-4) during the course of the study

(🖫 Abb. 06-01-04-04 and 06-01-04-20)

Table 34: Creatinine during the study

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
Creatinine (mg/dl)	1:Bas	N	21	14	35

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
Visit	Statistic			
	MEAN	7.74	8.37	7.99
	STD	2.47	3.28	2.79
	MIN	4.90	3.20	3.20
	Q1	6.00	6.00	6.00
	MEDIAN	7.10	6.60	6.90
	Q3	8.90	11.20	10.20
	MAX	15.10	14.20	15.10
	P			0.6737
2:W1	N	21	14	35
	MEAN	3.53	3.18	3.39
	STD	3.40	2.11	2.92
	MIN	1.00	1.20	1.00
	Q1	1.90	1.90	1.90
	MEDIAN	2.60	2.15	2.30
	Q3	3.60	4.30	3.90
	MAX	14.80	7.60	14.80
	P			0.9731
3:W2	N	21	14	35
	MEAN	3.08	2.86	2.99
	STD	3.14	2.19	2.77
	MIN	1.10	1.10	1.10
	Q1	1.60	1.70	1.60
	MEDIAN	2.10	1.90	2.00
	Q3	2.50	2.60	2.60
	MAX	13.30	7.70	13.30
	P			0.9865
4:W3	N	21	13	34
	MEAN	2.31	2.17	2.26
	STD	1.86	0.74	1.52
	MIN	1.10	1.40	1.10
	Q1	1.50	1.50	1.50
	MEDIAN	1.70	2.00	1.85
	Q3	2.30	2.40	2.40
	MAX	8.70	4.00	8.70
	P			0.3369
5:W4	N	21	14	35
	MEAN	1.94	1.67	1.83
	STD	1.34	0.33	1.06
	MIN	1.00	1.10	1.00
	Q1	1.30	1.50	1.40
	MEDIAN	1.70	1.70	1.70

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
Visit	Statistic			
	Q3	2.00	1.80	2.00
	MAX	7.50	2.40	7.50
	P			0.8260
6:W12	N	21	14	35
	MEAN	1.80	1.50	1.68
	STD	0.88	0.21	0.70
	MIN	1.00	1.10	1.00
	Q1	1.20	1.40	1.30
	MEDIAN	1.70	1.50	1.50
	Q3	2.00	1.60	1.80
	MAX	5.00	1.90	5.00
	P			0.3172
7:M6	N	21	14	35
	MEAN	1.70	1.46	1.60
	STD	0.68	0.28	0.56
	MIN	1.00	1.00	1.00
	Q1	1.20	1.30	1.20
	MEDIAN	1.50	1.45	1.50
	Q3	2.00	1.60	1.90
	MAX	3.70	2.00	3.70
	P			0.4880
8:M12	N	21	14	35
	MEAN	1.73	1.39	1.59
	STD	0.93	0.25	0.75
	MIN	0.90	0.80	0.80
	Q1	1.20	1.30	1.20
	MEDIAN	1.60	1.40	1.50
	Q3	1.80	1.50	1.70
	MAX	4.60	1.70	4.60
	P			0.3703

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-04-22-01)

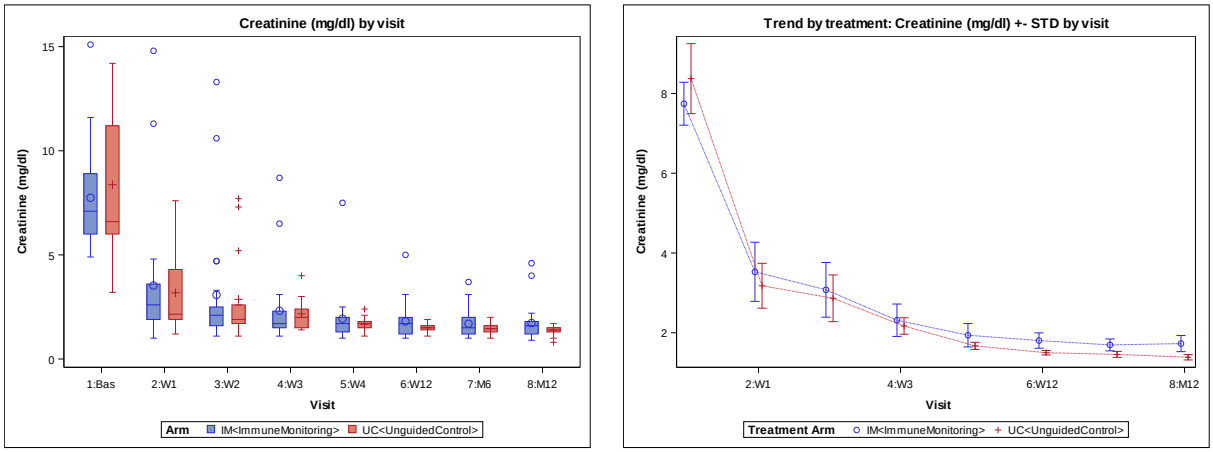

Figure 7: Creatinine during the course of the study

(🖫 Abb. 06-01-04-01 and 06-01-04-18)

Table 35: Creatinine clearance (Cockroft Gault) during the study

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
Crea-Cl.(Cockroft Gault) [ml/min/1.73m²]	1:Bas	N	21	14	35
		MEAN	12.60	12.61	12.61
		STD	3.09	4.89	3.84
		MIN	6.90	6.13	6.13
		Q1	10.49	9.07	9.82
		MEDIAN	12.56	12.41	12.56
		Q3	15.30	14.48	15.09
		MAX	18.24	23.99	23.99
		P			0.7747
	2:W1	N	21	14	35
		MEAN	40.72	38.79	39.94
		STD	22.56	17.29	20.36
		MIN	6.27	12.21	6.27
		Q1	22.67	17.76	21.79
		MEDIAN	36.53	41.89	38.94
		Q3	54.77	50.95	52.55
		MAX	81.21	66.48	81.21
		P			0.8268
	3:W2	N	21	14	35
		MEAN	44.99	45.49	45.19
		STD	20.43	20.84	20.29
		MIN	6.98	10.46	6.98
		Q1	32.69	37.93	32.69

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	45.72	47.21	47.03
		Q3	64.31	61.16	64.31
		MAX	75.23	75.48	75.48
		P			0.8006
	4:W3	N	21	13	34
		MEAN	50.20	46.16	48.66
		STD	18.11	13.83	16.50
		MIN	10.06	19.09	10.06
		Q1	44.18	40.16	41.25
		MEDIAN	47.69	46.74	47.59
		Q3	60.18	56.41	59.48
		MAX	82.30	71.32	82.30
		P			0.3211
	5:W4	N	21	14	35
		MEAN	54.80	56.37	55.43
		STD	16.76	10.93	14.54
		MIN	11.59	31.82	11.59
		Q1	45.31	50.22	46.29
		MEDIAN	50.08	55.66	53.72
		Q3	67.54	65.16	66.64
		MAX	87.73	72.72	87.73
		P			0.6017
	6:W12	N	21	14	35
		MEAN	56.36	61.60	58.46
		STD	16.03	10.45	14.13
		MIN	15.62	43.56	15.62
		Q1	48.05	53.59	50.34
		MEDIAN	53.82	58.62	56.97
		Q3	67.85	72.34	72.34
		MAX	84.92	75.68	84.92
		P			0.3044
	7:M6	N	20	14	34
		MEAN	58.50	65.04	61.20
		STD	17.27	13.63	15.99
		MIN	19.67	45.83	19.67
		Q1	48.01	52.62	49.08
		MEDIAN	55.10	66.74	60.84
		Q3	71.22	75.70	74.00
		MAX	89.17	84.62	89.17
		P			0.2411
	8:M12	N	21	14	35

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEAN	60.15	68.73	63.59
		STD	18.45	15.25	17.53
		MIN	17.79	44.50	17.79
		Q1	50.92	55.72	52.65
		MEDIAN	61.64	68.89	65.97
		Q3	71.50	76.28	75.07
		MAX	96.02	98.27	98.27
		P			0.1835

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-04-22-02)

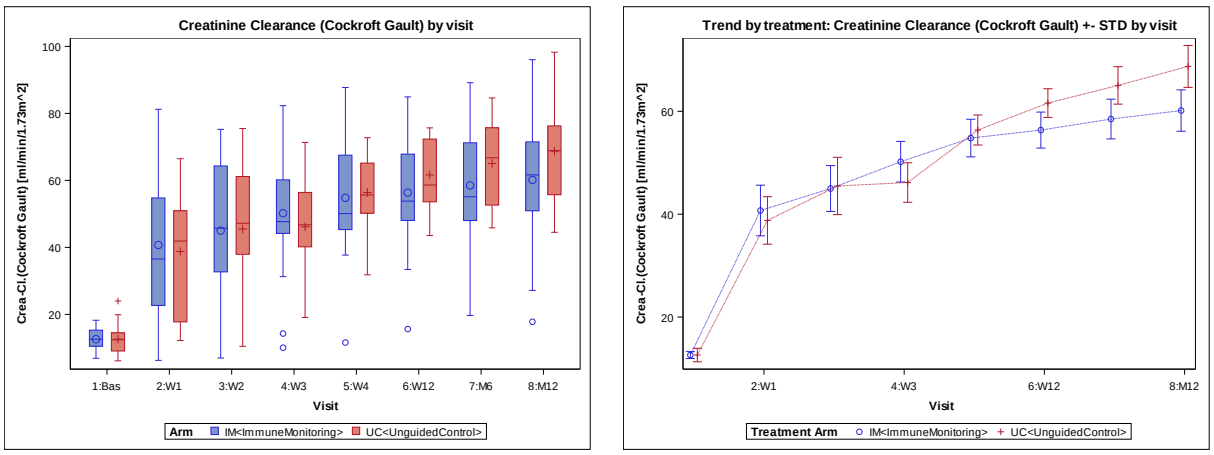

Figure 8: eCRF (Cockroft Gault) during the study

(🖫 Abb. 06-01-04-18)

Table 36: eGFR (Nankivell) during the study

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
eGFR (Nankivell) [ml/min/1.73m²]	1:Bas	N	21	14	35
		MEAN	15.50	18.70	16.78
		STD	9.22	3.97	7.65
		MIN	-5.77	10.12	-5.77
		Q1	9.64	15.07	10.12
		MEDIAN	20.78	20.26	20.28
		Q3	22.08	21.87	22.05
		MAX	26.57	23.58	26.57

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		P			0.8006
	2:W1	N	21	14	35
		MEAN	42.74	40.02	41.65
		STD	22.47	15.74	19.84
		MIN	6.60	11.64	6.60
		Q1	28.18	28.65	28.18
		MEDIAN	34.44	41.96	38.56
		Q3	53.21	51.36	52.08
		MAX	85.37	65.48	85.37
		P			0.9597
	3:W2	N	21	14	35
		MEAN	45.93	43.52	44.96
		STD	19.52	19.67	19.32
		MIN	4.43	4.69	4.43
		Q1	38.58	38.08	38.08
		MEDIAN	45.54	47.31	47.23
		Q3	58.30	53.82	58.30
		MAX	78.94	71.16	78.94
		P			0.9329
	4:W3	N	21	13	34
		MEAN	50.89	46.74	49.30
		STD	16.37	10.74	14.44
		MIN	9.16	26.12	9.16
		Q1	45.41	42.94	44.08
		MEDIAN	52.34	48.63	49.48
		Q3	60.55	51.02	57.42
		MAX	77.66	64.26	77.66
		P			0.3950
	5:W4	N	21	14	35
		MEAN	56.12	56.76	56.38
		STD	14.35	7.29	11.90
		MIN	15.88	43.56	15.88
		Q1	47.66	53.50	50.74
		MEDIAN	56.53	55.62	56.45
		Q3	66.85	62.07	63.96
		MAX	84.67	71.18	84.67
		P			0.8006
	6:W12	N	21	14	35
		MEAN	57.27	61.22	58.85
		STD	14.00	5.93	11.52
		MIN	23.07	52.94	23.07

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		Q1	49.04	57.78	52.95
		MEDIAN	56.49	59.60	58.59
		Q3	68.22	62.09	66.63
		MAX	83.41	77.37	83.41
		P			0.2191
	7:M6	N	20	14	34
		MEAN	58.91	63.33	60.73
		STD	14.89	9.23	12.89
		MIN	27.42	47.64	27.42
		Q1	49.96	57.78	52.01
		MEDIAN	58.74	61.68	60.66
		Q3	65.44	69.49	68.59
		MAX	84.12	80.38	84.12
		P			0.2858
	8:M12	N	21	14	35
		MEAN	60.64	66.59	63.02
		STD	16.01	12.04	14.66
		MIN	25.42	57.40	25.42
		Q1	51.94	58.58	57.40
		MEDIAN	59.84	62.56	61.17
		Q3	66.58	69.59	69.59
		MAX	92.47	101.67	101.67
		P			0.2888

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-04-22-03)

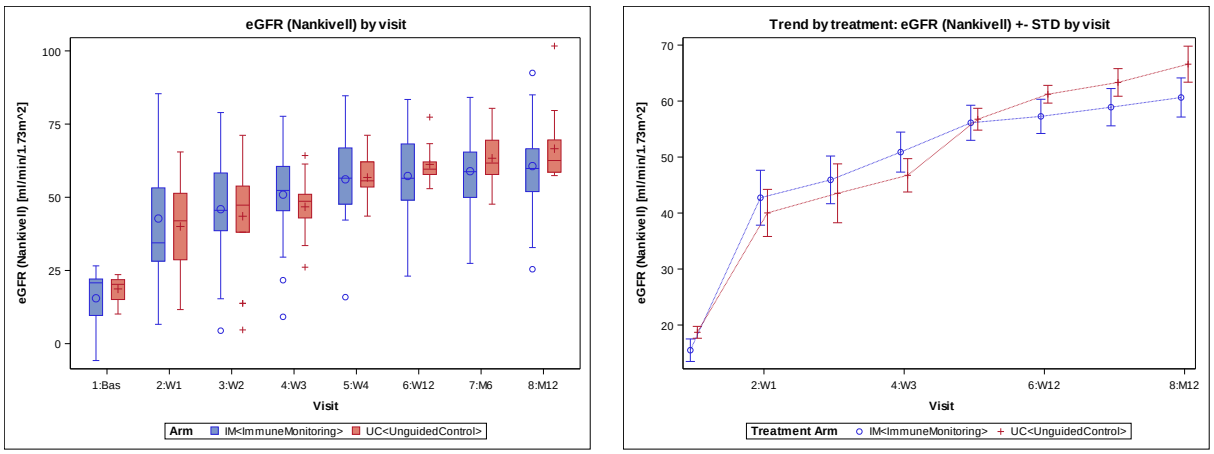

Figure 9: eCRF (Nankivell) during the study

(🖫 Abb. 06-01-04-19)

Table 37: eGFR (CKD-EPI) during the study

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
eGFR (CKD-EPI) [ml/min/1.73m^2]	1:Bas	N	21	14	35
		MEAN	8.17	8.33	8.23
		STD	2.33	3.92	3.01
		MIN	3.78	3.81	3.78
		Q1	6.59	5.31	6.04
		MEDIAN	8.49	8.41	8.49
		Q3	9.21	10.01	10.01
		MAX	12.54	18.64	18.64
		P			0.8006
	2:W1	N	21	14	35
		MEAN	35.16	32.43	34.07
		STD	23.50	16.57	20.78
		MIN	3.79	7.58	3.79
		Q1	18.16	13.96	16.95
		MEDIAN	27.02	32.47	30.96
		Q3	46.79	43.68	46.28
		MAX	81.61	61.02	81.61
		P			0.8796
	3:W2	N	21	14	35
		MEAN	39.19	38.80	39.04
		STD	19.73	19.31	19.28
		MIN	4.31	7.36	4.31
		Q1	29.68	31.45	29.68
		MEDIAN	39.87	40.39	39.87
		Q3	53.86	50.75	53.86
		MAX	71.21	67.79	71.21
		P			0.9597
	4:W3	N	21	13	34
		MEAN	44.59	39.57	42.67
		STD	17.23	13.01	15.74
		MIN	6.53	15.24	6.53
		Q1	35.71	34.97	34.97
		MEDIAN	44.01	37.17	43.34
		Q3	58.19	46.59	53.51
		MAX	72.72	65.61	72.72
		P			0.3041
	5:W4	N	21	14	35

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEAN	49.32	50.66	49.86
		STD	15.73	10.65	13.76
		MIN	7.81	28.26	7.81
		Q1	40.58	43.68	41.70
		MEDIAN	46.46	50.85	50.75
		Q3	64.10	57.69	62.90
		MAX	72.93	67.79	72.93
		P			0.7747
	6:W12	N	21	14	35
		MEAN	50.64	56.49	52.98
		STD	15.44	9.32	13.49
		MIN	12.75	42.88	12.75
		Q1	41.00	49.50	43.49
		MEDIAN	50.24	53.68	52.57
		Q3	63.97	65.61	64.10
		MAX	72.93	74.12	74.12
		P			0.2190
	7:M6	N	21	14	35
		MEAN	53.31	59.67	55.86
		STD	16.71	13.29	15.55
		MIN	18.22	37.79	18.22
		Q1	43.49	46.70	44.42
		MEDIAN	50.24	59.18	57.69
		Q3	64.10	74.12	68.73
		MAX	81.61	78.00	81.61
		P			0.3206
	8:M12	N	21	14	35
		MEAN	54.88	63.28	58.24
		STD	18.53	15.41	17.61
		MIN	14.00	42.58	14.00
		Q1	44.68	50.04	48.84
		MEDIAN	56.56	60.53	57.78
		Q3	65.45	71.41	70.57
		MAX	82.26	98.93	98.93
		P			0.2453

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 06-01-04-22-05)

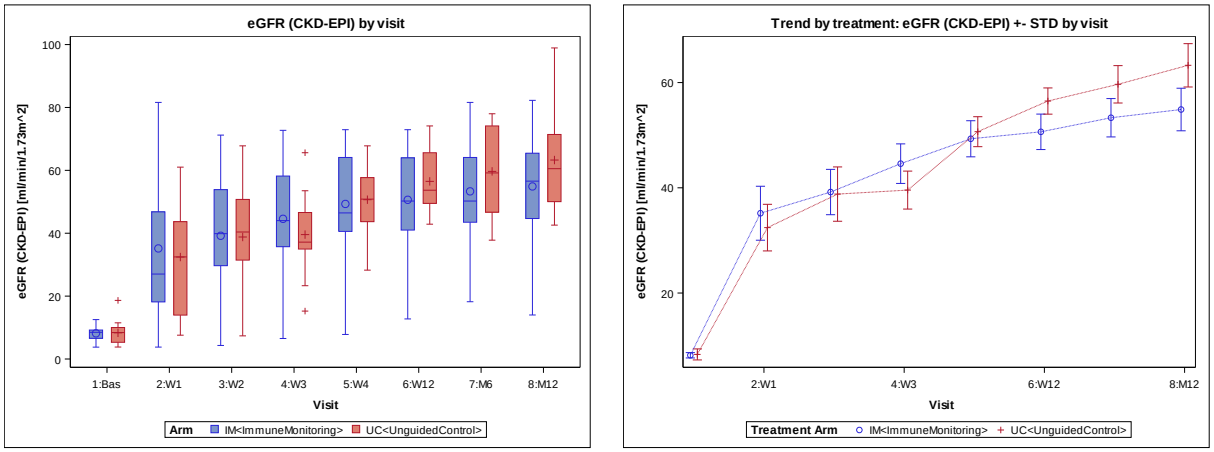

Figure 10: eCRF (CKD-EPI) during the study

(🖫 Abb. 06-01-04-21)

12.5.1.2.3 Renal function changes during the study

Changes of renal function parameters were evaluated in relation to several starting points for all the follow up visits. The results are in accordance with the course of the renal function parameters displayed in the figures above. When compared to the day-14 values no significant differences were found between the immune monitored group and the unguided control group.

Table 38: eGFR(MDRD-4) change from day 14 (Visit 3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFD14 eGFR (MDRD-4) [ml/min/1.73 m2]	4:W3	N	21	13	34
		MEAN	5.18	2.31	4.08
		STD	8.89	10.36	9.43
		MIN	-11.57	-18.78	-18.78
		Q1	0.00	-5.87	0.00
		MEDIAN	5.93	2.21	5.06
		Q3	10.66	9.99	10.66
		MAX	22.38	15.75	22.38
		P			0.5232
	5:W4	N	21	14	35
		MEAN	9.55	11.28	10.24
		STD	11.65	14.78	12.81
		MIN	-7.56	-4.00	-7.56
		Q1	0.00	0.00	0.00

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	9.70	7.18	8.43
		Q3	14.42	19.46	17.78
		MAX	38.99	45.45	45.45
		P			1.0000
	6:W12	N	21	14	35
		MEAN	10.83	16.84	13.23
		STD	13.07	17.46	15.03
		MIN	-6.31	-6.35	-6.35
		Q1	0.00	6.21	0.00
		MEDIAN	6.50	13.64	8.43
		Q3	22.38	28.96	23.85
		MAX	41.80	50.40	50.40
		P			0.3199
	7:M6	N	21	14	35
		MEAN	13.36	19.66	15.88
		STD	14.49	14.23	14.52
		MIN	-6.31	6.78	-6.31
		Q1	1.99	9.78	6.78
		MEDIAN	13.15	12.56	13.15
		Q3	18.66	28.96	26.27
		MAX	47.67	55.65	55.65
		P			0.2738
	8:M12	N	21	14	35
		MEAN	14.73	22.87	17.98
		STD	16.26	15.95	16.40
		MIN	-12.06	4.30	-12.06
		Q1	4.45	10.95	6.02
		MEDIAN	13.62	17.41	16.06
		Q3	22.97	31.67	31.67
		MAX	46.56	55.65	55.65
		P			0.2320

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-25-01-04)

Table 39: Creatinine change from day 14 (Visit 3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFD14 Creatinine (mg/dl)	4:W3	N	21	13	34

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEAN	-0.76	-0.80	-0.78
		STD	1.56	1.62	1.56
		MIN	-6.80	-4.70	-6.80
		Q1	-0.80	-0.60	-0.80
		MEDIAN	-0.20	-0.10	-0.15
		Q3	0.00	0.20	0.00
		MAX	0.20	0.40	0.40
		P			0.5342
	5:W4	N	21	14	35
		MEAN	-1.14	-1.19	-1.16
		STD	2.53	2.04	2.31
		MIN	-11.40	-5.90	-11.40
		Q1	-0.80	-0.90	-0.90
		MEDIAN	-0.30	-0.25	-0.30
		Q3	0.00	0.00	0.00
		MAX	0.30	0.10	0.30
		P			0.8658
	6:W12	N	21	14	35
		MEAN	-1.27	-1.36	-1.31
		STD	2.70	2.15	2.46
		MIN	-11.50	-6.20	-11.50
		Q1	-1.00	-0.90	-1.00
		MEDIAN	-0.20	-0.45	-0.40
		Q3	0.00	-0.20	0.00
		MAX	0.10	0.10	0.10
		P			0.5775
	7:M6	N	21	14	35
		MEAN	-1.38	-1.41	-1.39
		STD	2.76	2.05	2.47
		MIN	-11.20	-5.70	-11.20
		Q1	-1.20	-1.00	-1.20
		MEDIAN	-0.30	-0.45	-0.40
		Q3	-0.10	-0.30	-0.20
		MAX	0.20	-0.10	0.20
		P			0.3447
	8:M12	N	21	14	35
		MEAN	-1.35	-1.48	-1.40
		STD	2.69	2.13	2.45
		MIN	-11.10	-6.30	-11.10
		Q1	-1.10	-1.20	-1.20
		MEDIAN	-0.30	-0.50	-0.50

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		Q3	-0.20	-0.30	-0.20
		MAX	0.70	-0.10	0.70
		P			0.3536

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-2501-01)

Table 40: Creatinine clearance (Cockroft Gault) change from day 14 (Visit 3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFD14 Crea-Cl.(Cockroft Gault) [mg/ml/1.73m2]	4:W3	N	21	13	34
		MEAN	5.21	1.87	3.93
		STD	8.95	11.75	10.07
		MIN	-12.41	-22.05	-22.05
		Q1	-0.29	-8.36	-1.06
		MEDIAN	5.03	1.60	4.66
		Q3	10.87	9.90	10.85
		MAX	25.53	18.29	25.53
		P			0.5707
	5:W4	N	21	14	35
		MEAN	9.81	10.88	10.24
		STD	11.81	15.65	13.27
		MIN	-8.02	-3.66	-8.02
		Q1	1.47	-1.21	-1.03
		MEDIAN	9.97	5.72	9.06
		Q3	12.59	19.67	18.99
		MAX	41.70	46.58	46.58
		P			0.7747
	6:W12	N	21	14	35
		MEAN	11.36	16.12	13.26
		STD	13.30	17.78	15.19
		MIN	-4.69	-9.00	-9.00
		Q1	0.80	6.21	1.01
		MEDIAN	6.65	10.78	8.67
		Q3	22.24	25.27	24.90
		MAX	45.99	49.77	49.77
		P			0.3545
	7:M6	N	20	14	34

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEAN	15.02	19.56	16.89
		STD	13.25	14.80	13.87
		MIN	-6.25	3.57	-6.25
		Q1	3.82	10.95	6.18
		MEDIAN	13.79	13.40	13.40
		Q3	23.45	26.20	26.20
		MAX	39.96	57.11	57.11
		P			0.5174
	8:M12	N	21	14	35
		MEAN	15.16	23.25	18.40
		STD	15.85	16.76	16.47
		MIN	-8.81	5.26	-8.81
		Q1	2.31	11.17	7.23
		MEDIAN	14.94	20.97	16.45
		Q3	27.29	32.60	31.02
		MAX	39.92	57.69	57.69
		P			0.2454

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-25 01-02)

Table 41: eGFR (Nankivell) change from day 14 (Visit 3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFD14 eGFR (Nankivell) [ml/min/1.73 m2]	4:W3	N	21	13	34
		MEAN	4.96	4.41	4.75
		STD	9.38	12.62	10.55
		MIN	-14.94	-20.86	-20.86
		Q1	0.56	-1.43	-0.17
		MEDIAN	5.98	1.40	5.35
		Q3	11.08	10.57	11.08
		MAX	23.07	28.81	28.81
		P			0.7498
	5:W4	N	21	14	35
		MEAN	10.20	13.23	11.41
		STD	11.68	17.50	14.13
		MIN	-10.34	-1.11	-10.34
		Q1	0.45	1.03	0.45

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	11.45	5.85	9.04
		Q3	14.31	21.25	18.37
		MAX	38.14	50.18	50.18
		P			0.9329
	6:W12	N	21	14	35
		MEAN	11.34	17.70	13.88
		STD	13.36	20.09	16.41
		MIN	-9.84	-6.37	-9.84
		Q1	1.57	3.59	1.57
		MEDIAN	5.31	13.91	12.58
		Q3	21.27	23.54	23.54
		MAX	41.16	54.69	54.69
		P			0.4288
	7:M6	N	20	14	34
		MEAN	14.34	19.81	16.59
		STD	14.07	17.09	15.38
		MIN	-11.16	5.92	-11.16
		Q1	3.59	8.45	5.92
		MEDIAN	14.10	10.22	13.20
		Q3	25.33	22.58	22.99
		MAX	42.86	57.89	57.89
		P			0.3722
	8:M12	N	21	14	35
		MEAN	14.71	23.07	18.06
		STD	15.52	18.70	17.11
		MIN	-15.20	5.26	-15.20
		Q1	2.37	9.23	5.70
		MEDIAN	15.55	12.75	14.16
		Q3	23.09	35.53	30.50
		MAX	40.25	57.38	57.38
		P			0.3206

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-25-01-03)

Table 42: eGFR (CKD-EPI) change from day 14 (Visit 3)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFD14 eGFR (CKD-EPI) [ml/min/1.73 m2]	4:W3	N	21	13	34
		MEAN	5.39	2.26	4.19
		STD	9.53	11.11	10.11
		MIN	-13.02	-21.20	-21.20
		Q1	0.00	-6.39	0.00
		MEDIAN	5.93	2.22	5.28
		Q3	11.24	10.59	11.24
		MAX	23.77	15.85	23.77
		P			0.5004
	5:W4	N	21	14	35
		MEAN	10.12	11.86	10.82
		STD	12.27	15.65	13.52
		MIN	-7.76	-4.37	-7.76
		Q1	0.00	0.00	0.00
		MEDIAN	10.41	7.35	9.09
		Q3	14.63	20.90	19.83
		MAX	41.00	48.91	48.91
		P			0.9731
	6:W12	N	21	14	35
		MEAN	11.45	17.69	13.94
		STD	13.84	18.35	15.84
		MIN	-7.11	-7.20	-7.20
		Q1	0.00	6.57	0.00
		MEDIAN	7.26	14.48	9.09
		Q3	23.77	30.33	25.36
		MAX	44.06	54.38	54.38
		P			0.2882
	7:M6	N	21	14	35
		MEAN	14.12	20.86	16.82
		STD	15.18	14.94	15.24
		MIN	-7.11	7.54	-7.11
		Q1	2.11	10.51	7.54
		MEDIAN	14.43	13.66	14.35
		Q3	20.98	30.33	28.01
		MAX	48.45	60.26	60.26
		P			0.2888
	8:M12	N	21	14	35
		MEAN	15.69	24.48	19.20
		STD	17.31	17.00	17.49
		MIN	-13.43	4.62	-13.43
		Q1	4.78	11.20	6.22

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	15.57	19.26	16.29
		Q3	25.19	34.56	33.55
		MAX	49.84	60.26	60.26
		P			0.2067

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-25-01-05)

When changes were calculated relative to the week 4 values, in eGFR the change to M12 is significantly larger in the UD group (MDRD-4: IM: 5.17±9.59; UC: 11.59±6.69; p=0.0161). A similar result is obtained for other renal function parameters.

Table 43: eGFR (MDRD-4) change from week 4 (visit 5)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFW4 eGFR (MDRD-4) [ml/min/1.73 m^2]	6:W12	N	21	14	35
		MEAN	1.27	5.56	2.99
		STD	6.85	8.62	7.79
		MIN	-14.77	-6.35	-14.77
		Q1	0.00	0.00	0.00
		MEDIAN	0.00	4.12	1.92
		Q3	4.97	9.99	6.78
		MAX	15.02	22.06	22.06
		P			0.2790
	7:M6	N	21	14	35
		MEAN	3.80	8.38	5.63
		STD	8.09	7.63	8.12
		MIN	-6.98	-4.88	-6.98
		Q1	0.00	2.50	0.00
		MEDIAN	2.29	8.53	6.03
		Q3	7.85	13.65	11.27
		MAX	20.70	22.06	22.06
		P			0.0883
	8:M12	N	21	14	35
		MEAN	5.17	11.59	7.74
		STD	9.59	6.69	9.02
		MIN	-13.41	3.11	-13.41
		Q1	2.46	6.62	3.30

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MEDIAN	4.60	11.20	6.62
		Q3	8.97	14.35	12.37
		MAX	32.87	27.10	32.87
		P			**0.0161**

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-26-01-04)

Table 44: Creatinine change from week 4 (visit 5)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFW4 Creatinine (mg/dl)	6:W12	N	21	14	35
		MEAN	-0.13	-0.17	-0.15
		STD	0.58	0.25	0.47
		MIN	-2.50	-0.70	-2.50
		Q1	-0.10	-0.30	-0.20
		MEDIAN	0.00	-0.10	-0.10
		Q3	0.00	0.00	0.00
		MAX	0.60	0.10	0.60
		P			0.3183
	7:M6	N	21	14	35
		MEAN	-0.24	-0.21	-0.23
		STD	0.85	0.24	0.67
		MIN	-3.80	-0.80	-3.80
		Q1	-0.20	-0.30	-0.30
		MEDIAN	-0.10	-0.20	-0.10
		Q3	0.00	-0.10	0.00
		MAX	0.60	0.20	0.60
		P			0.2484
	8:M12	N	21	14	35
		MEAN	-0.21	-0.29	-0.24
		STD	0.75	0.17	0.58
		MIN	-2.90	-0.70	-2.90
		Q1	-0.20	-0.30	-0.30
		MEDIAN	-0.10	-0.20	-0.20
		Q3	-0.10	-0.20	-0.10
		MAX	1.50	-0.10	1.50
		P			**0.0424**

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2 P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions					

🖫 Abb. 06-01-04-26-01-01)

Table 45: Creatinine clearance (Cockroft Gault) change from week 4 (visit 5)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFW4 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m^2]	6:W12	N	21	14	35
		MEAN	1.55	5.23	3.03
		STD	7.61	8.57	8.09
		MIN	-16.67	-6.24	-16.67
		Q1	0.26	-0.62	-0.15
		MEDIAN	2.32	3.34	2.64
		Q3	4.96	10.04	7.11
		MAX	17.39	21.96	21.96
		P			0.6373
	7:M6	N	20	14	34
		MEAN	4.63	8.67	6.30
		STD	7.24	7.69	7.59
		MIN	-7.52	-3.15	-7.52
		Q1	0.33	1.90	0.34
		MEDIAN	4.17	8.43	6.19
		Q3	8.42	14.38	12.28
		MAX	16.99	21.40	21.40
		P			0.2015
	8:M12	N	21	14	35
		MEAN	5.35	12.36	8.16
		STD	9.25	7.07	9.03
		MIN	-14.76	2.54	-14.76
		Q1	0.84	6.37	4.81
		MEDIAN	5.92	11.31	8.22
		Q3	8.72	17.02	12.94
		MAX	27.33	25.55	27.33
		P			**0.0193**

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-26-01-02)

Table 46: eGFR (Nankivell) change from week 4 (visit 5)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFW4 eGFR (Nankivell) [ml/min/1.73 m²]	6:W12	N	21	14	35
		MEAN	1.14	4.46	2.47
		STD	6.35	7.14	6.78
		MIN	-15.70	-6.39	-15.70
		Q1	-1.26	-0.23	-0.56
		MEDIAN	1.38	3.44	1.73
		Q3	4.86	8.65	5.73
		MAX	14.89	17.94	17.94
		P			0.3206
	7:M6	N	20	14	34
		MEAN	3.64	6.57	4.85
		STD	7.28	6.12	6.88
		MIN	-7.95	-3.09	-7.95
		Q1	-1.23	0.48	-0.44
		MEDIAN	2.47	7.55	4.29
		Q3	8.31	9.91	9.39
		MAX	17.31	16.98	17.31
		P			0.2015
	8:M12	N	21	14	35
		MEAN	4.52	9.83	6.64
		STD	8.18	7.14	8.11
		MIN	-9.39	3.63	-9.39
		Q1	1.42	4.20	2.29
		MEDIAN	3.31	8.18	5.12
		Q3	9.54	13.13	11.55
		MAX	27.48	30.49	30.49
		P			**0.0211**

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-26-01-03)

Table 47: eGFR (CKD-EPI) change from week 4 (visit 5)

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFW4 eGFR (CKD-EPI) [ml/min/1.73 m²]	6:W12	N	21	14	35
		MEAN	1.32	5.82	3.12

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		STD	7.55	9.20	8.42
		MIN	-16.67	-7.20	-16.67
		Q1	0.00	0.00	0.00
		MEDIAN	0.00	4.48	2.07
		Q3	4.94	10.59	7.26
		MAX	17.03	23.18	23.18
		P			0.2640
	7:M6	N	21	14	35
		MEAN	4.00	9.00	6.00
		STD	8.67	8.06	8.67
		MIN	-7.45	-5.13	-7.45
		Q1	0.00	2.65	0.00
		MEDIAN	2.49	9.55	6.21
		Q3	8.65	14.88	12.39
		MAX	21.28	23.18	23.18
		P			0.0709
	8:M12	N	21	14	35
		MEAN	5.56	12.61	8.38
		STD	10.38	7.69	9.91
		MIN	-14.22	3.15	-14.22
		Q1	2.67	6.56	3.63
		MEDIAN	4.81	12.40	6.64
		Q3	10.16	15.24	13.72
		MAX	35.37	31.14	35.37
		P			**0.0211**

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-26-01-05)

Evaluating the change from month 3 overall shows small improvements, but no significant differences between the treatment groups.

Table 48: eGFR (MDRD-4) change from month 3

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM3 eGFR (MDRD-4) [ml/min/1.73m^2]	7:M6	N	21	14	35
		MEAN	2.53	2.81	2.64
		STD	6.55	7.73	6.94

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MIN	-7.56	-14.87	-14.87
		Q1	0.00	0.00	0.00
		MEDIAN	2.29	3.60	3.57
		Q3	7.25	5.25	7.25
		MAX	14.96	13.65	14.96
		P			0.8132
	8:M12	N	21	14	35
		MEAN	3.90	6.03	4.75
		STD	8.87	11.87	10.06
		MIN	-9.82	-18.01	-18.01
		Q1	-2.97	-0.20	-0.36
		MEDIAN	3.27	4.81	4.36
		Q3	8.24	12.21	9.64
		MAX	22.71	33.45	33.45
		P			0.6494

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-27-01-04)

Table 49: Creatinine change from month 3

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM3 Creatinine (mg/dl)	7:M6	N	21	14	35
		MEAN	-0.11	-0.04	-0.08
		STD	0.32	0.20	0.28
		MIN	-1.30	-0.30	-1.30
		Q1	-0.20	-0.10	-0.20
		MEDIAN	-0.10	-0.10	-0.10
		Q3	0.00	0.00	0.00
		MAX	0.30	0.50	0.50
		P			0.7213
	8:M12	N	21	14	35
		MEAN	-0.08	-0.11	-0.09
		STD	0.32	0.18	0.27
		MIN	-0.50	-0.40	-0.50
		Q1	-0.30	-0.30	-0.30
		MEDIAN	-0.10	-0.10	-0.10
		Q3	0.10	0.00	0.00
		MAX	0.90	0.30	0.90

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		P			0.9057

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-27-01-01)

Table 50: Creatinine clearance (Cockroft Gault) change from month 3

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM3 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m²]	7:M6	N	20	14	34
		MEAN	3.12	3.44	3.25
		STD	6.52	7.57	6.86
		MIN	-8.63	-13.20	-13.20
		Q1	-0.17	0.93	0.00
		MEDIAN	3.14	4.07	3.89
		Q3	7.52	7.33	7.33
		MAX	16.55	15.26	16.55
		P			0.8201
	8:M12	N	21	14	35
		MEAN	3.80	7.13	5.13
		STD	9.21	11.17	10.02
		MIN	-9.35	-14.10	-14.10
		Q1	-2.30	0.23	-0.57
		MEDIAN	2.22	6.17	2.69
		Q3	9.92	13.56	13.15
		MAX	23.41	31.78	31.78
		P			0.4691

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-27-01-02)

Table 51: eGFR (Nankivell) change from month 3

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM3 eGFR (Nankivell) [ml/min/1.73 m²]	7:M6	N	20	14	34
		MEAN	2.37	2.11	2.26
		STD	5.36	6.85	5.92

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MIN	-6.58	-11.74	-11.74
		Q1	-1.32	-0.96	-1.31
		MEDIAN	2.48	2.40	2.40
		Q3	7.10	5.15	6.46
		MAX	11.53	15.59	15.59
		P			0.9025
	8:M12	N	21	14	35
		MEAN	3.37	5.37	4.17
		STD	7.39	11.73	9.26
		MIN	-8.73	-14.32	-14.32
		Q1	-3.00	-0.38	-1.08
		MEDIAN	3.28	2.18	2.69
		Q3	7.23	8.49	8.49
		MAX	18.36	36.88	36.88
		P			0.7747

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-27-01-03)

Table 52: eGFR (CKD-EPI) change from month 3

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM3 eGFR (CKD-EPI) [ml/min/1.73 m^2]	7:M6	N	21	14	35
		MEAN	2.68	3.18	2.88
		STD	7.07	8.37	7.50
		MIN	-8.22	-15.72	-15.72
		Q1	0.00	0.00	0.00
		MEDIAN	2.49	3.82	3.64
		Q3	7.83	5.88	7.83
		MAX	15.22	14.94	15.22
		P			0.7357
	8:M12	N	21	14	35
		MEAN	4.24	6.79	5.26
		STD	9.72	13.29	11.16
		MIN	-10.69	-19.13	-19.13
		Q1	-3.19	-0.35	-0.41
		MEDIAN	3.55	5.27	4.66
		Q3	9.33	13.44	10.52

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MAX	24.48	38.34	38.34
		P			0.6494

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-27-01-05)

The changes in relation to month 6 are even smaller and no significant differences between treatment arms were detected.

Table 53: eGFR (MDRD-4) change from month 6

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM6 eGFR (MDRD-4) [ml/min/1.73 m^2]	8:M12	N	21	14	35
		MEAN	1.37	3.21	2.11
		STD	6.05	10.28	7.92
		MIN	-8.33	-18.01	-18.01
		Q1	-2.77	-3.76	-3.76
		MEDIAN	0.00	3.50	0.00
		Q3	5.77	8.57	6.62
		MAX	13.10	20.32	20.32
		P			0.4690

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-28-01-04)

Table 54: Creatinine change from month 6

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM6 Creatinine (mg/dl)	8:M12	N	21	14	35
		MEAN	0.03	-0.07	-0.01
		STD	0.32	0.22	0.28
		MIN	-0.40	-0.60	-0.60
		Q1	-0.10	-0.20	-0.20
		MEDIAN	0.00	-0.10	0.00
		Q3	0.10	0.10	0.10

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
		MAX	0.90	0.30	0.90
		P			0.3336

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-28-01-01)

Table 55: Creatinine clearance (Cockroft Gault) change from month 6

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM6 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m^2]	8:M12	N	20	14	34
		MEAN	1.34	3.69	2.31
		STD	6.14	9.82	7.81
		MIN	-8.03	-15.03	-15.03
		Q1	-3.22	-3.51	-3.32
		MEDIAN	0.52	3.87	0.73
		Q3	7.53	9.16	8.31
		MAX	11.64	20.17	20.17
		P			0.4518

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-04-28-01-02)

Table 56: eGFR (Nankivell) change from month 6

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM6 eGFR (Nankivell) [ml/min/1.73 m^2]	8:M12	N	20	14	34
		MEAN	1.44	3.26	2.19
		STD	4.99	9.03	6.87
		MIN	-5.49	-13.35	-13.35
		Q1	-2.13	-2.75	-2.26
		MEDIAN	0.60	3.46	1.31
		Q3	5.29	6.95	6.95
		MAX	10.16	21.29	21.29
		P			0.6618

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2 P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions					

(🖫 Abb. 06-01-04-28-01-03)

Table 57: eGFR (CKD-EPI) change from month 6

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Visit	Statistic			
CFM6 eGFR (CKD-EPI) [ml/min/1.73 m^2]	8:M12	N	21	14	35
		MEAN	1.56	3.61	2.38
		STD	6.55	11.25	8.64
		MIN	-8.62	-19.13	-19.13
		Q1	-3.02	-3.99	-3.99
		MEDIAN	0.00	3.90	0.00
		Q3	6.54	9.44	7.32
		MAX	14.08	23.39	23.39
		P			0.4899
P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2 P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions					

(🖫 Abb. 06-01-04-28-01-05)

12.5.1.2.4 Deaths and Graft Failures

No death and no graft failure has been reported in any patient within the 12 months study period.

12.5.1.2.5 Rejections

A total of 16 rejections have been reported, 11 in the immune monitored group and 5 in the unguided control group. 7 rejections were graded Banff 4, 8 were Banff 3 and in one case the grading is missing. On a per patient basis 8/21 patients (38.10%) in the IM group and 5/14 patients (35.71%) in the UC group had at least one rejection. Regarding BPARs only it was 7/21 (33.33%) and 5/14 (35.71%) respectively. The result is the same for tBPAR. Banff4 rejections were recorded in 3/21 (14.29%) in the IM and 4/14 (28.57%) in the UC group (Table 58).

Table 58: Patient rejection summary

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
Has Rejection(s)	No	N(%)	13 (61.9)	9 (64.3)	22 (62.9)
	Yes	N(%)	8 (38.1)	5 (35.7)	13 (37.1)
		P			1.0000
Has BPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
Has tBPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
Has BANFF 4	No	N(%)	18 (85.7)	10 (71.4)	28 (80.0)
	Yes	N(%)	3 (14.3)	4 (28.6)	7 (20.0)
		P			0.4007

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Tab. 05-01-05-05)

All time dependent analysis were based on the first occurrence of a rejection and calculated as time span from the day of transplantation. The time to rejection (Table 59, Figure 11), time to BPAR (Table 60, Figure 12), and time to first Banff 4 rejection (Table 61, Figure 13) did not show any significant difference between the treatment groups.

Table 59: Time to rejection over strata

IM<Immune monitoring>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	9.000	.
25	9.000	5.000	.
Mean	42.333	Standard Error	5.352

UC<Unguided control>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	6.000	.
25	7.000	5.000	.
Mean	7.357	Standard Error	0.331

Summary of the Number of Censored and Uncensored Values

Stratum	RndArm	Total	Failed	Censored	Percent Censored
1	IM<ImmuneMonitoring>	21	8	13	61.90
2	UC<UnguidedControl>	14	5	9	64.29
Total		35	13	22	62.86

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0008	1	0.9772

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
RndArm	IM	1	-0.02230	0.57037	0.0015	0.9688	0.978	0.320	2.991

(🖫 Tab. 05-01-05-07-03,04)

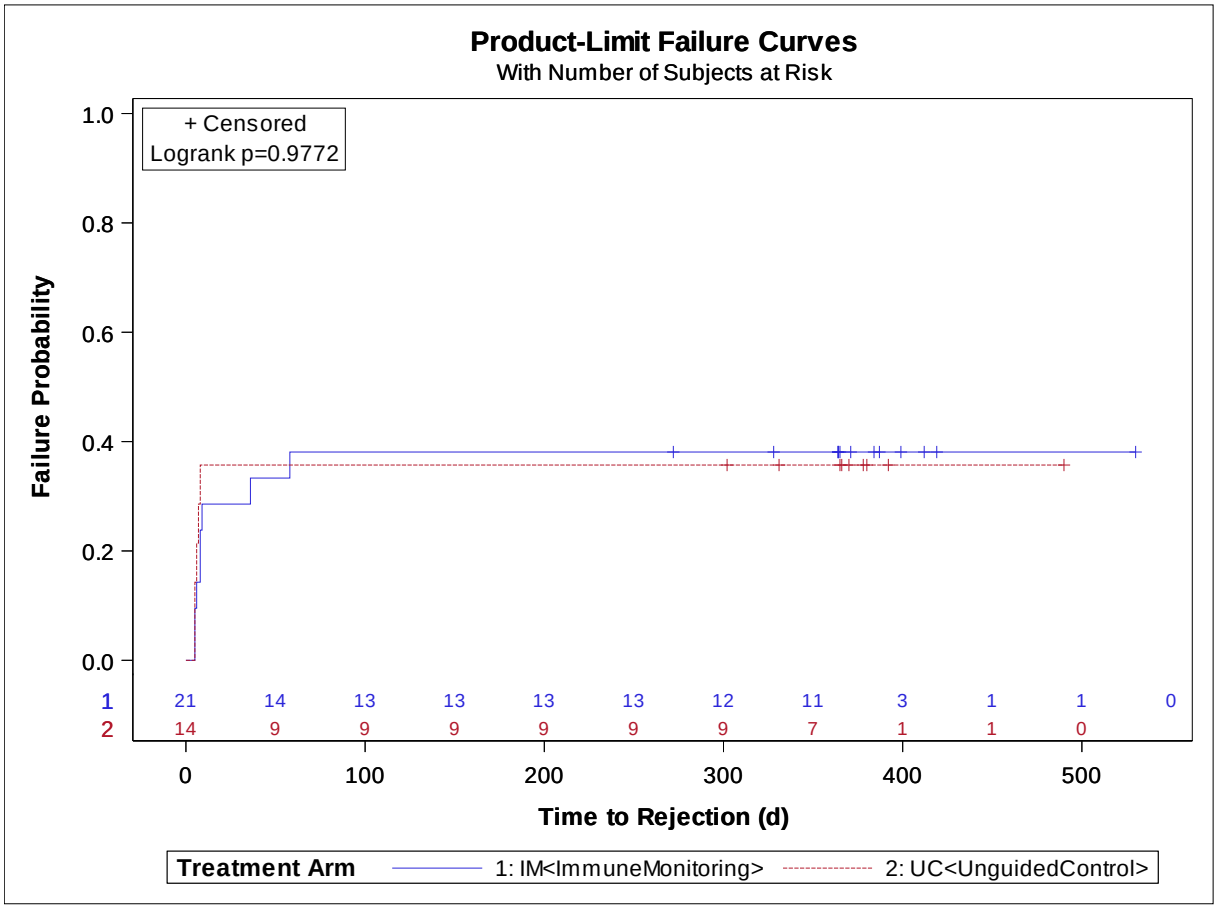

Figure 11: Failure plot for time to first rejection

(🖫 Tab. 05-01-05-07-03)

Table 60: Time to BPAR over strata

IM<Immune monitoring>				
Quartile Estimates				
Percent	Point Estimate	95% Confidence Interval	[Lower	Upper)
75	.		.	.
50	.		36.000	.
25	36.000		5.000	.
Mean	44.857	Standard Error	5.084	

UC<Unguided control>				
Quartile Estimates				
Percent	Point Estimate	95% Confidence Interval	[Lower	Upper)
75	.		.	.

IM<Immune monitoring>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
50	.	6.000	.
25	7.000	5.000	.

Mean	7.357	Standard Error	0.331

Summary of the Number of Censored and Uncensored Values

Stratum	RndArm	Total	Failed	Censored	Percent Censored
1	IM<ImmuneMonitoring>	21	7	14	66.67
2	UC<UnguidedControl>	14	5	9	64.29
Total		35	12	23	65.71

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.1201	1	0.7290

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
RndArm	IM	1	-0.20840	0.58598	0.1265	0.7221	0.812	0.257	2.560

(🖫 Tab. 05-01-05-07-09, 10)

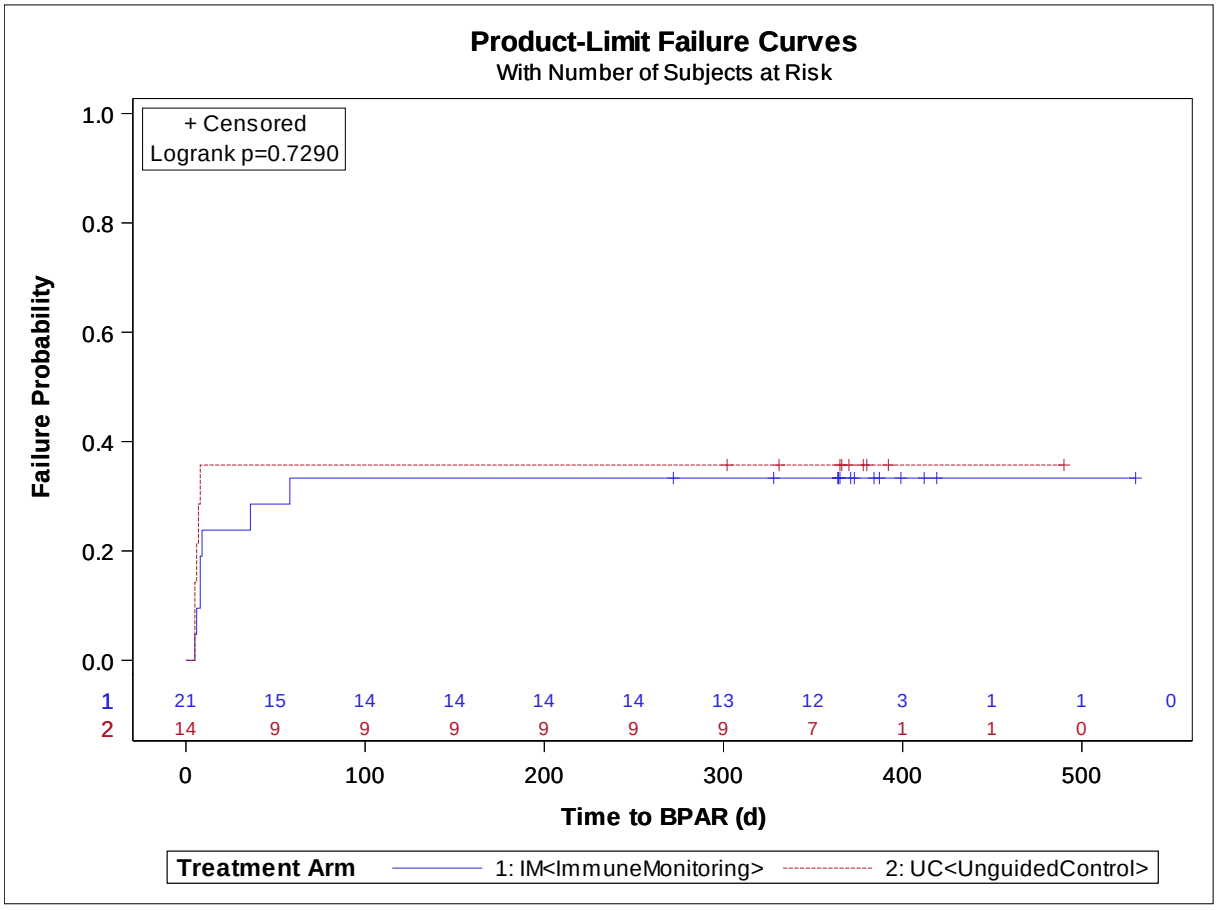

Figure 12: Failure plot for time to first BPAR

(🖫 Tab. 05-01-05-07-09)

Table 61: Time to Banff 4 over strata

IM<Immune monitoring>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval	[Lower	Upper)
75	.		.	.
50	.		.	.
25	.		6.000	.
Mean	228.714	Standard Error	19.182	

UC<Unguided control>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval	[Lower	Upper)
75	.		.	.
50	.		6.000	.

25	7.000		5.000	.
Mean	6.643	Standard Error	0.222	

Summary of the Number of Censored and Uncensored Values

Stratum	RndArm	Total	Failed	Censored	Percent Censored
1	IM<ImmuneMonitoring>	21	3	18	85.71
2	UC<UnguidedControl>	14	4	10	71.43
Total		35	7	28	80.00

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.3026	1	0.2537

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
RndArm	IM	1	-0.85315	0.76450	1.2454	0.2644	0.426	0.095	1.906

(🖫 Tab. 05-01-05-07-15, 16)

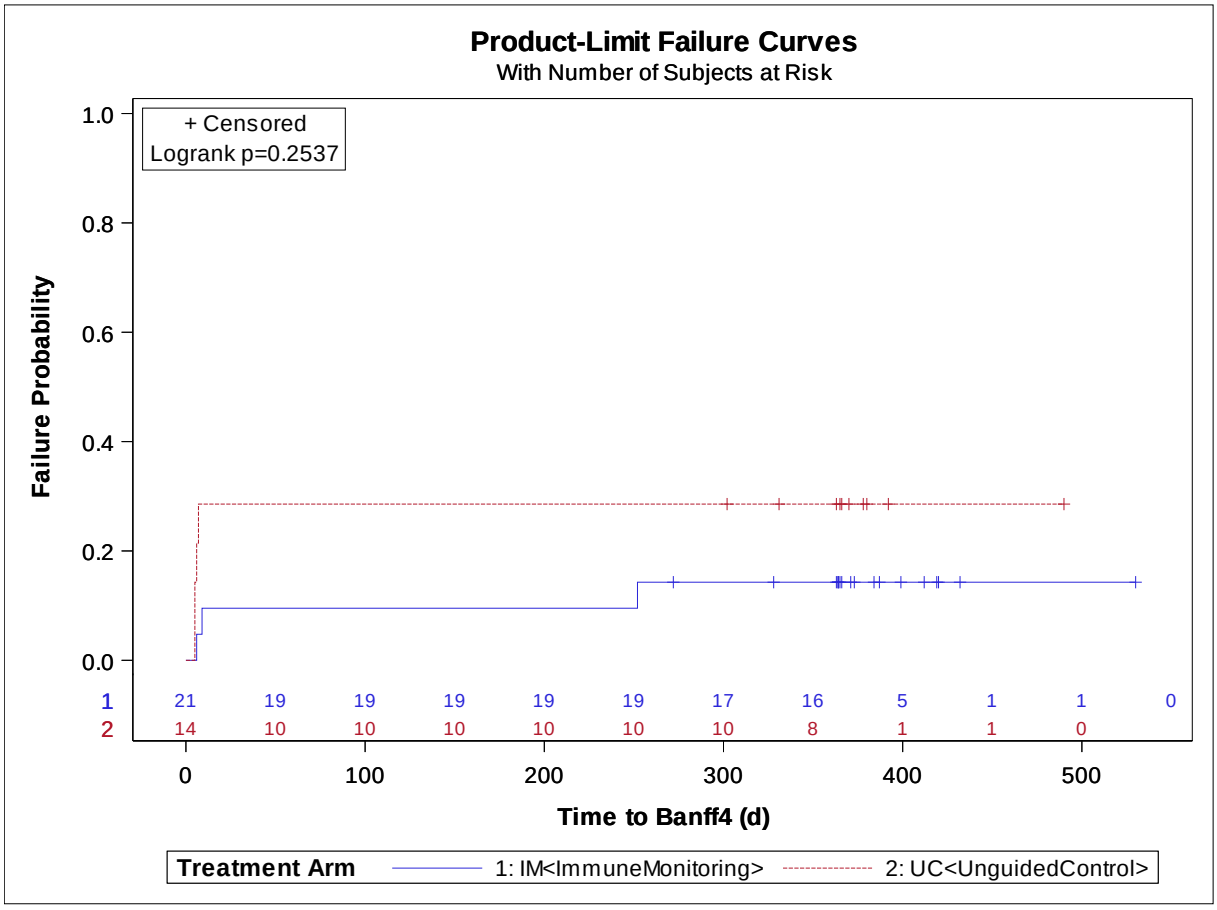

Figure 13: Failure plot for time to first Banff 4

(🖫 Tab. 05-01-05-07-15)

12.5.1.2.6 Treatment failures

Treatment failures were analysed in three ways:

a) an immunological failure is considered a patient who had either donor specific HLA antibodies detected or a positive INFγ assay or has a biopsy proven rejection. The parameter is not very well suited to distinguish treatment arms as the criteria are met by most of the patients (85.7% in the IM and 100.0% in the UC arm). Therefore no result is statistically significant but the proportions are slightly higher in the UC group (Table 62).

b) a treatment failure was defined as a patient with BPAR or discontinuation of study treatment. No difference between treatment groups was found by this parameter (Table 63).

c) a composite efficacy treatment failure was defined as p patient who had a BPAR or a eGFR according to the MDRD 4-variable formula below 50 ml/min/1.73m^2. This parameter also shows no difference between the treatment groups (Table 64).

Time to event analysis by Kaplan Meier analyses supports the result obtained for the proportions and does not show statistical significance by use of the Logrank test (Table 65 - Table 66). The curve for the immunological failure suggests less events in the IM group, but the difference is not significant and does not translate to better renal function.

Table 62: Immunological failures

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
Has post-BL DSA	No	N(%)	20 (95.2)	10 (71.4)	30 (85.7)
	Yes	N(%)	1 (4.8)	4 (28.6)	5 (14.3)
		P			0.1336
Has post-BL INFy	No	N(%)	4 (19.0)	1 (7.1)	5 (14.3)
	Yes	N(%)	17 (81.0)	13 (92.9)	30 (85.7)
		P			0.6272
Has BPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
Has post-BL DSA/INFy/BPAR	No	N(%)	3 (14.3)		3 (8.6)
	Yes	N(%)	18 (85.7)	14 (100.0)	32 (91.4)
		P			0.2588

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-05-04c)

Table 63: Treatment failures

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
BPAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
Discontinuation	No	N(%)	19 (90.5)	14 (100.0)	33 (94.3)
	Yes	N(%)	2 (9.5)		2 (5.7)
		P			0.5059
Treatment failure	No	N(%)	13 (61.9)	9 (64.3)	22 (62.9)
	Yes	N(%)	8 (38.1)	5 (35.7)	13 (37.1)
		P			1.0000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-05.05)

Table 64: Composite efficacy treatment failure

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
		Statistic			
PBAR	No	N(%)	14 (66.7)	9 (64.3)	23 (65.7)
	Yes	N(%)	7 (33.3)	5 (35.7)	12 (34.3)
		P			1.0000
MDRD-4 < 50 ml/min/1.73m^2	No	N(%)	13 (61.9)	11 (78.6)	24 (68.6)
	Yes	N(%)	8 (38.1)	3 (21.4)	11 (31.4)
		P			0.4606
Composite efficacy failure	No	N(%)	11 (52.4)	7 (50.0)	18 (51.4)
	Yes	N(%)	10 (47.6)	7 (50.0)	17 (48.6)
		P			1.0000

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-05.06)

Table 65: Time to immunological failure

IM<Immune monitoring>

Quartile Estimates

		95% Confidence Interval	
Percent	Point Estimate	[Lower	Upper)
75	83.000	34.000	.
50	33.000	20.000	77.000
25	20.000	5.000	28.000
Mean	49.190	Standard Error	8.422

UC<Unguided control>

Quartile Estimates

		95% Confidence Interval	
Percent	Point Estimate	[Lower	Upper)
75	43.000	26.000	282.000
50	26.000	6.000	43.000
25	7.000	5.000	26.000
Mean	43.429	Standard Error	18.925

Summary of the Number of Censored and Uncensored Values

Stratum	RndArm	Total	Failed	Censored	Percent Censored
1	IM<ImmuneMonitoring>	21	18	3	14.29
2	UC<UnguidedControl>	14	14	0	0.00
Total		35	32	3	8.57

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	3.0546	1	0.0805

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
RndArm	IM	1	-0.63663	0.36595	3.0264	0.0819	0.529	0.258	1.084

(🖫 Abb. 06-01-05-07)

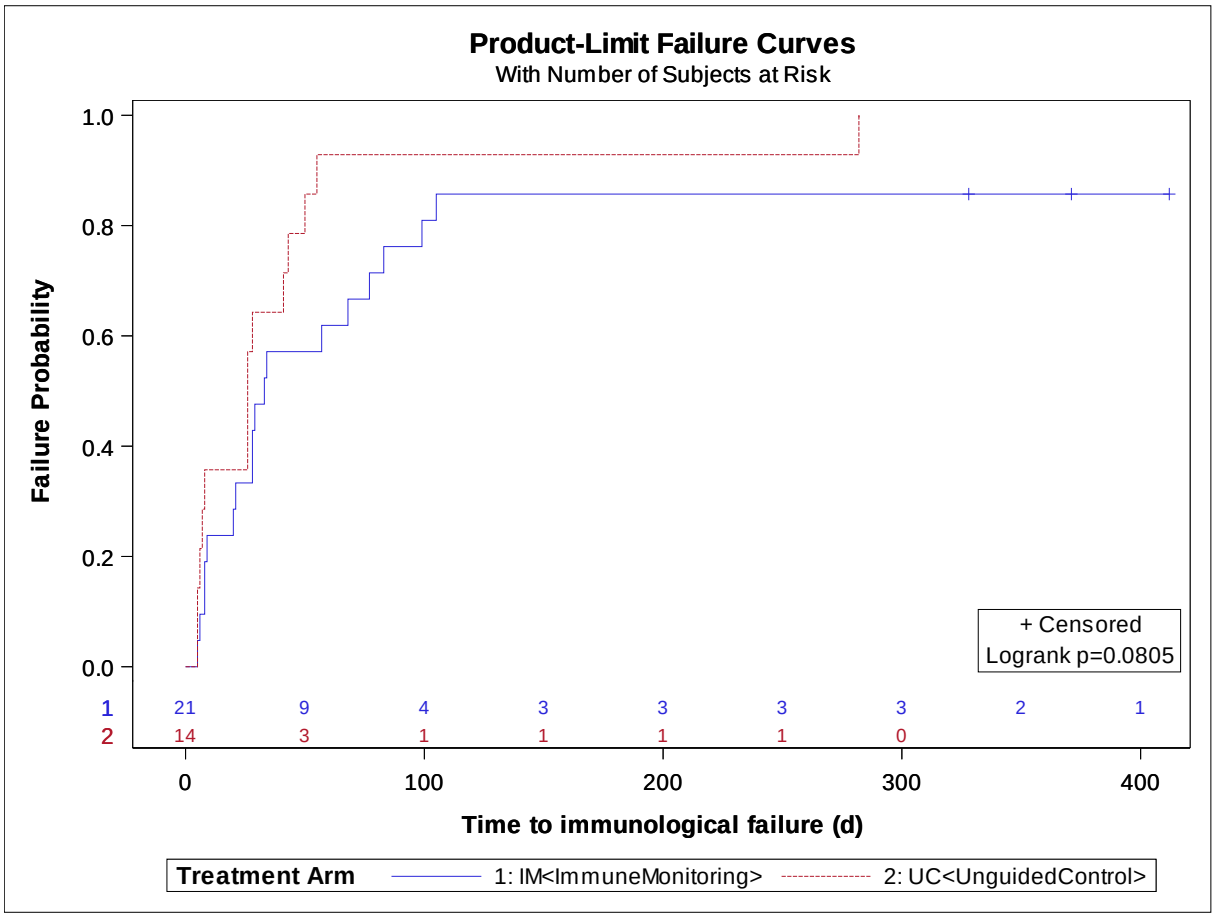

Figure 14: Time to immunological failure

(🖫 Abb. 06-01-05-07)

Table 66: Time to treatment failure

IM<Immune monitoring>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	13.000	.
25	13.000	5.000	.
Mean	42.714	Standard Error	5.220

UC<Unguided control>

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	.	.	.
50	.	6.000	.
25	7.000	5.000	.
Mean	7.357	Standard Error	0.331

Summary of the Number of Censored and Uncensored Values

Stratum	RndArm	Total	Failed	Censored	Percent Censored
1	IM<ImmuneMonitoring>	21	8	13	61.90
2	UC<UnguidedControl>	14	5	9	64.29
Total		35	13	22	62.86

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0106	1	0.9178

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
RndArm	IM	1	-0.06666	0.57053	0.0137	0.9070	0.936	0.306 2.862

(🖫 Abb. 06-01-05-11,12)

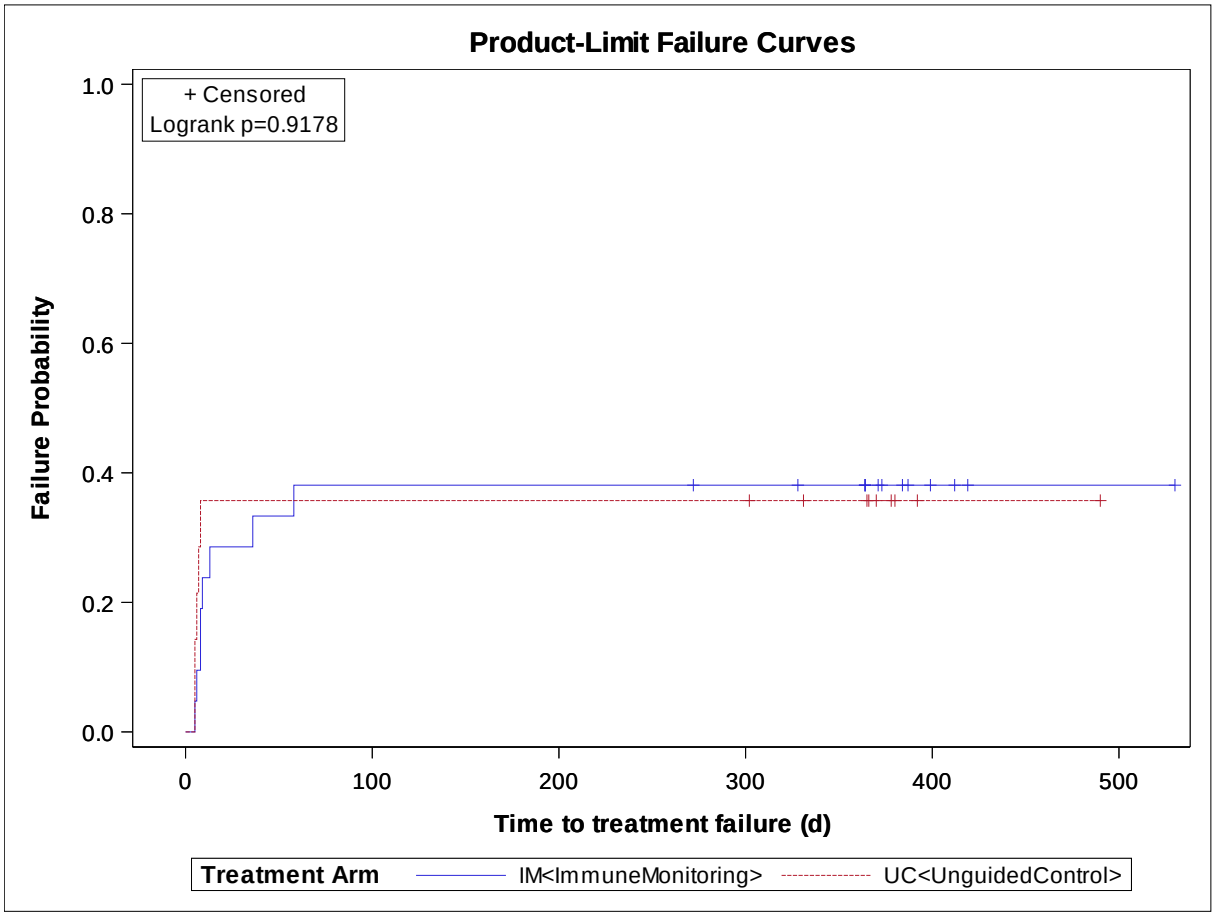

Figure 15: Time to treatment failure

(🖫 Abb. 06-01-05-11)

12.5.2 Tumors during the study

During the study only one tumor was diagnosed in the immune monitoring group (multiple new skin malignoma detected 198 days after transplantation; pat. #013). No tumors occurred in the unguided control.

12.5.3 Pre-Planned Supportive Analyses

12.5.4 Subgroup analysis

Pre-planned subgroup analysis included analysis by sex and age at transplantation (<60, vs ≥60 years). Starting from the total sample size of 35 patients, significant results were not expected in the subgroups.

The female sub-group is with a sample size of only 8 relatively small but when comparing the primary endpoint eGFR(MDRD-4) after 12 months in female to male patients a significant difference was found in favour of female recipients (female (mean±SD): 66.85±12.22 vs. male: 52.54±15.28; p=0.0113) (Table 67). Other renal function endpoints show also a highly significant difference between female and male recipients (Table 06-01-02-09-02 in the appendix).

Analysing the sub-groups of male and female patients in the IM vs. the UC group, the result is numerically in favour of the unguided control in female as well as in male patients, but the results are not statistical significant (Table 68).

Table 67: eGFR (MDRD-4) by sex

		Sex		
		Female	Male	Total
	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	N	8	27	35
	NMISS	0	0	0
	MEAN	66.85	52.54	55.81
	STD	12.22	15.28	15.70
	LCLM	56.64	46.49	50.42
	UCLM	77.07	58.58	61.20
	MIN	53.95	14.57	14.57
	Q1	57.28	43.77	47.99
	MEDIAN	63.19	52.85	55.32
	Q3	75.21	62.20	65.95
	MAX	89.51	80.47	89.51
	P			0.0113

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-02-09-01)

Table 68: eGFR (MDRD-4) analysed in subgroups by sex

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Sex	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	Female	N	6	2	8
		NMISS	0	0	0
		MEAN	63.23	77.73	66.85
		STD	9.51	16.66	12.22
		LCLM	53.25	-71.97	56.64
		UCLM	73.21	227.44	77.07
		MIN	53.95	65.95	53.95
		Q1	57.28	65.95	57.28
		MEDIAN	58.85	77.73	63.19

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Sex	Statistic			
		Q3	75.13	89.51	75.21
		MAX	75.30	89.51	89.51
		P			0.2405
	Male	N	15	12	27
		NMISS	0	0	0
		MEAN	48.31	57.82	52.54
		STD	17.57	10.21	15.28
		LCLM	38.58	51.33	46.49
		UCLM	58.04	64.30	58.58
		MIN	14.57	43.77	14.57
		Q1	41.25	49.46	43.77
		MEDIAN	47.99	56.34	52.85
		Q3	53.85	62.31	62.20
		MAX	76.26	80.47	80.47
		P			0.0603

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-02-10-01)

Analysing the pre-defined subgroups resulted in a very small group of only 3 patients in the age of 60+ and the result is highly influenced by one patient with an eGFR of 71.63 ml/min/1.73m^2. Due to the exclusion of this patient from the group < 60 years of age, the difference between the IM and UC group became significant but the result should not be overestimated (Table 69).

As an alternative equal spaced age groups were compared. Besides the expected fact that younger patients had better renal functions after 12 months the previously seen difference in eGFR in favour of the unguided control can be seen throughout the age groups (Table 70).

Table 69: eGFR (MDRD-4) in age subgroups below and greater equal 60

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Age group	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	1:18-59	N	20	12	32
		NMISS	0	0	0
		MEAN	51.62	62.94	55.86
		STD	16.78	12.24	16.02
		LCLM	43.77	55.16	50.09
		UCLM	59.47	70.71	61.64
		MIN	14.57	48.18	14.57

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Age group	Statistic			
		Q1	42.97	55.50	48.09
		MEDIAN	53.35	61.08	55.50
		Q3	58.85	67.91	64.19
		MAX	76.26	89.51	89.51
		P			0.0373
	2:>=60	N	1	2	3
		NMISS	0	0	0
		MEAN	71.63	47.00	55.21
		STD	.	4.58	14.58
		LCLM	.	5.89	18.99
		UCLM	.	88.11	91.43
		MIN	71.63	43.77	43.77
		Q1	71.63	43.77	43.77
		MEDIAN	71.63	47.00	50.24
		Q3	71.63	50.24	71.63
		MAX	71.63	50.24	71.63
		P			0.5403

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-02-11-01)

Table 70: eGFR (MDRD-4) in equal spaced age subgroups

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Age group	Statistic			
eGFR (MDRD-4) [ml/min/1.73m^2]	1:<30	N	6	4	10
		NMISS	0	0	0
		MEAN	60.83	75.51	66.70
		STD	10.95	11.97	13.11
		LCLM	49.34	56.47	57.33
		UCLM	72.32	94.56	76.08
		MIN	47.99	62.20	47.99
		Q1	53.95	66.03	57.28
		MEDIAN	57.28	75.17	66.03
		Q3	73.37	84.99	75.13
		MAX	75.13	89.51	89.51
		P			0.1087
	2:30-39	N	9	5	14
		NMISS	0	0	0

			Treatment Arm		
			IM<ImmuneMon	UC<UnguidedC	Total
	Age group	Statistic			
		MEAN	48.58	58.44	52.10
		STD	16.00	6.85	14.00
		LCLM	36.28	49.94	44.01
		UCLM	60.88	66.94	60.18
		MIN	18.36	48.18	18.36
		Q1	42.85	55.67	43.09
		MEDIAN	52.85	59.96	53.85
		Q3	53.85	62.42	60.43
		MAX	75.30	65.95	75.30
		P			0.1420
	3:40-49	N	2	1	3
		NMISS	0	0	0
		MEAN	45.42	57.02	49.28
		STD	43.62	.	31.57
		LCLM	-346.54	.	-29.13
		UCLM	437.37	.	127.70
		MIN	14.57	57.02	14.57
		Q1	14.57	57.02	14.57
		MEDIAN	45.42	57.02	57.02
		Q3	76.26	57.02	76.26
		MAX	76.26	57.02	76.26
		P			1.0000
	4:50-59	N	3	2	5
		NMISS	0	0	0
		MEAN	46.47	52.00	48.68
		STD	4.88	4.70	5.16
		LCLM	34.36	9.78	42.28
		UCLM	58.59	94.22	55.09
		MIN	41.25	48.68	41.25
		Q1	41.25	48.68	47.26
		MEDIAN	47.26	52.00	48.68
		Q3	50.91	55.32	50.91
		MAX	50.91	55.32	55.32
		P			0.3865
	5:60-69	N	1	2	3
		NMISS	0	0	0
		MEAN	71.63	47.00	55.21
		STD	.	4.58	14.58
		LCLM	.	5.89	18.99
		UCLM	.	88.11	91.43
		MIN	71.63	43.77	43.77

		Treatment Arm		
		IM<ImmuneMon	UC<UnguidedC	Total
Age group	Statistic			
	Q1	71.63	43.77	43.77
	MEDIAN	71.63	47.00	50.24
	Q3	71.63	50.24	71.63
	MAX	71.63	50.24	71.63
	P			0.5403

P(numeric): Wilcoxon rank sum test (k=2 groups) or Kruskal Wallis if k> 2
P(categorial): Fishers exact test (2x2tables) or Chi square test in higher dimensions

(🖫 Abb. 06-01-02-12-01)

12.5.5 Summary of Efficacy Results and Conclusions

The following table lists the primary efficacy parameter together with sensitivity analyses (Table 71). While numerical smaller eGFR values can be seen in the IM group, no statistically significant difference was found for the eGFR 12 months after transplantation between the immune monitored patients compared to the unguided control group. Various sensitivity analyses support this result. The result of the per protocol analysis agrees well with the ITT analysis (with a bit smaller absolute values).

The secondary endpoints at 12 months post transplantation also show no significant differences between the treatment groups, despite the eGFR change between week 4 up to month 12 where significant results were observed for all renal function parameters with a larger improvement in the unguided control compared to the immune monitored group.

All biopsy proven rejection (BPAR) were treated in the study and therefore the result for tBPAR is the same. Overall, 12 patients (34.3%) have reported at least one BPAR (7 (33.3%) in the IM group and 5 (35.7%) in the UC group; p=1.0000).

No patient died and no graft failure was reported during the study. Only on tumor has been reported. The sample size is too small and/or the follow up period too small to detect a possible difference between the study arms in these parameters.

After premature termination of the study no significant differences in efficacy parameters could be detected between the immune monitored group and the unguided control group. Renal function parameters at 12 months suggest that even with the planned sample size a demonstration of an advantage of the immune monitored group is not very likely. It should be kept in mind, that the current result can not prove the hypothesis that immune monitoring will result in a better eGFR(MDRD-4) than unguided control but it does not prove that there is no difference.

Table 71: Primary endpoint summary

			IM		UC		P
Parameter	Population	Test	N	Mean±SD (95% CI)	N	Mean±SD (95% CI)	P

Primary analysis							
eGFR(MDRD-4) [ml/min/1.73m^2]	ITT	Wilcoxon rank sum test	21	52.57±16.92 (44.87-60.28)	14	60.66±12.72 (53.32-68.01)	0.1524
Sensitivity analysis							
eGFR(MDRD-4) [ml/min/1.73m^2]	ITT	TTest (eq. variances)	21	52.57±16.92 (44.87-60.28)	14	52.57±16.92 (44.87-60.28)	0.1377
eGFR(MDRD-4) [ml/min/1.73m^2]	Mod. ITT 1)	Wilcoxon rank sum test	19	56.38±12.56 (50.32-62.43)	14	60.66±12.72 (53.32-68.01)	0.2991
eGFR(MDRD-4) [ml/min/1.73m^2]	Mod. ITT 2)	Wilcoxon rank sum test	15	52.30±19.00 (41.78-62.82)	12	61.52±13.62 (52.87-70.18)	0.2133
eGFR(MDRD-4) [ml/min/1.73m^2]	PP	Wilcoxon rank sum test	11	47.33±19.23 (34.41-60.24)(	8	57.15±9.10 (49.54-64.76)	0.1731

1) Extremely low eGFR excluded

2) Delayed M12 excluded

Table 72: Summary of secondary endpoints (ITT)

		IM (N=21)	UC (N=14	
Parameter	Test	Mean±SD or N(%)	Mean±SD or N(%)	P
Renal function at M12				
Creatinine (mg/dl)	Wilcoxon rank sum test	1.73±0.93	1.39±0.25	0.3703
Crea-Cl.(Cockroft Gault) [ml/min/1.73 m2]	Wilcoxon rank sum test	60.15±18.45	68.73±15.25	0.1835
eGFR (Nankivell) [ml/min/1.73 m2]	Wilcoxon rank sum test	60.64±16.01	66.59±12.04	0.2888
eGFR (CKD-EPI) [ml/min/1.73m2]	Wilcoxon rank sum test	54.88±18.53	63.28±15.41	0.2453
Renal function failure rates at M12				
S-Cr >1.5 mg/dl	Fishers exact test	11 (52.4)	3 (21.4)	0.0885
S-Cr >2.0 mg/dl	Fishers exact test	3 (14.3)	0	0.2588
S-Cr CFM3 > 0.3 mg/dl	Fishers exact test	2 (9.5)	0	0.5059
S-Cr CFM6 > 0.3 mg/dl	Fishers exact test	2 (9.5)	0	0.5059
MDRD-4 < 50 ml/min/1.73m2	Fishers exact test	8 (38.1)	3 (21.4)	0.4606
MDRD-4 CFM3 < -10 ml/min/1.73m2	Fishers exact test	0	1 (7.1)	0.4000
MDRD-4 CFM6 < -10 ml/min/1.73m_	Fishers exact test	0	1 (7.1)	0.4000
Change from day 14 to M12				
CFD14 eGFR (MDRD-4) [ml/min/1.73 m2]	Wilcoxon rank sum test	14.73±16.26	22.87±15.95	0.2320
CFD14 Creatinine (mg/dl)	Wilcoxon rank sum test	-1.35±2.69	-1.48±2.13	0.3536
CFD14 Crea-Cl.(Cockroft Gault) [mg/ml/1.73m2]	Wilcoxon rank sum test	15.16±15.85	23.25±16.76	0.2454
CFD14 eGFR (Nankivell)	Wilcoxon rank sum test	14.71±15.52	23.07±18.70	0.3206

[ml/min/1.73 m2]				
CFD14 eGFR (CKD-EPI) [ml/min/1.73 m2]	Wilcoxon rank sum test	15.69±17.31	24.48±17.00	0.2067
Change from week4 to M12				
CFW4 eGFR (MDRD-4) [ml/min/1.73 m2]	Wilcoxon rank sum test	5.17±9.59	11.59±6.69	**0.0161**
CFW4 Creatinine (mg/dl)	Wilcoxon rank sum test	-0.21±0.75	-0.29±0.29	**0.0424**
CFW4 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m2]	Wilcoxon rank sum test	5.35±9.25	12.36±7.07	**0.0193**
CFW4 eGFR (Nankivell) [ml/min/1.73 m2]	Wilcoxon rank sum test	4.52±8.18	9.83±7.14	**0.0211**
CFW4 eGFR (CKD-EPI) [ml/min/1.73 m2]	Wilcoxon rank sum test	5.56±10.38	12.61±7.69	**0.0211**
Change from M3 to M12				
CFM3 eGFR (MDRD-4) [ml/min/1.73m2]	Wilcoxon rank sum test	3.90±8.87	6.03±11.87	0.6494
CFM3 Creatinine (mg/dl)	Wilcoxon rank sum test	-0.08±0.32	-0.11±0.18	0.9057
CFM3 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m2]	Wilcoxon rank sum test	3.80±9.21	7.13±11.17	0.4691
CFM3 eGFR (Nankivell) [ml/min/1.73 m2]	Wilcoxon rank sum test	3.37±7.39	5.37±11.73	0.7747
CFM3 eGFR (CKD-EPI) [ml/min/1.73 m2]	Wilcoxon rank sum test	4.24±9.72	6.79±13.29	0.6494
Change from M6 to M12				
CFM6 eGFR (MDRD-4) [ml/min/1.73m2]	Wilcoxon rank sum test	1.37±6.05	3.21±10.28	0.4690
CFM6 Creatinine (mg/dl)	Wilcoxon rank sum test	0.03±0.32	-0.07±0.22	0.3336
CFM6 Crea-Cl.(Cockroft Gault) [mg/ml/1.73 m2]	Wilcoxon rank sum test	1.34±6.14	3.69±9.82	0.4518
CFM6 eGFR (Nankivell) [ml/min/1.73 m2]	Wilcoxon rank sum test	1.44±4.99	3.26±9.03	0.6618
CFM6 eGFR (CKD-EPI) [ml/min/1.73 m2]	Wilcoxon rank sum test	1.56±6.55	3.61±11.25	0.4899
Death graft failure and tumors				
Death		None	None	-
Graft failure		None	None	-
Tumor		1 (4.8)	0	-
Rejections				
Any rejection	Fishers exact test	8 (38.1)	5 (35.7)	1.0000
Time to rjection	Logrank test	HR=0.978(0.320-2.991) *)		0.9772
BPAR		7 (33.3)	5 (35.7)	1.0000
Time to BPAR	Logrank test	HR=0.812(0.257-2.560) *)		0.7290
tBPAR		7 (33.3)	5 (35.7)	1.0000
Time to tBPAR	Logrank test	HR=0.812(0.257-2.560) *)		0.7290
Banff 4		3 (14.3)	4 (28.6)	0.4007
Time to Banff 4	Logrank test	HR= 0.426(0.095-1.906)*)		0.2537
Treatment failures				

Has post-BL DSA/INFy/BPAR	Fishers exact test	18 (85.7)	14 (100.0)	0.2588
Time to DSA/INFy/BPAR	Logrank test	HR=0.529(0.258-1.084) *)		0.0805
Treatment failure	Fishers exact test	8 (38.1)	5 (35.7)	1.0000
Time to treatment failure	Logrank test	HR=0.936 (0.306-2.862) *)		0.9178
Composite efficacy failure	Fishers exact test	10 (47.6)	7 (50.0)	1.0000

*) Hazard ratio for IM (95% CI); Median not reached.

13 SAFETY ANALYSES

The Safety population includes all patients who had taken at least one dose of the study medication and have an investigator contact afterwards. In this study no patient was excluded from the safety analyses and the safety population is identical to the ITT population.

13.1 Adverse Events

13.1.1 Brief Summary of Adverse Events

Adverse events were assessed after inclusion of the patients and until the end of study at the 12 months visit. A total of 211 adverse events were reported, most of them were mild (64%) to moderate (35%) in intensity. Only 23% of the reported events were considered possibly related to study medication. 21 out of 211 adverse events were serious adverse events as defined in the protocol and 7 were serious adverse reactions.

In general, adverse events and serious adverse events were as expected for this patient population. No significant difference was found between the treatment arms.

13.1.2 Display of Adverse Events

Adverse events were analysed by the MedDRA coded event term on the PT and SOC level, and the severity graded mild, moderate, severe and the causal relationship to the study product as assessed by the investigator.

A total of 211 adverse events have been reported, 146 (69%) in the immune monitored group and 65 (31%) in the unguided control group.

64% of the reported adverse events were mild, 35% were of moderate intensity and only 1% were of severe grade (Table 73). The two AE with severe intensity (post procedural haemorrhage and Generalised tonic-clonic seizure) are listed in Table 74.

Most AE were not related to study treatment (77%) and only 23% were considered as possibly related to study treatment by the investigator (Table 75). They will be described in section 13.1.3.1 in more detail.

From the total of 211 adverse events 21 (10%) were serious adverse events (SAE), 12 (8%) in the IM group and 9 (14%) in the unguided control (Table 76). They will be described in section 13.2.

Grouping the events by SOCs shows the majority of AEs in the SOC Investigations (19%), followed by Infections and infestations (15%) and gastrointestinal disorders (10%) (Table 77).

A detailed listing of all adverse events is provided in the Appendix.

Table 73: Severity of adverse events

	Group					
	IM		UC		All	
	N	PctN	N	PctN	N	PctN
Grade						
1-Mild	92	63.01	43	66.15	135	63.98
2-Moderate	54	36.99	20	30.77	74	35.07
3-Severe	.	.	2	3.08	2	0.95
All	146	100.00	65	100.00	211	100.00

(🖫 Tab. 08-01-02-00a)

Table 74: List of AE with severe intensity

Site-Id	Pat-ID	AE Term	Start Date(e)	Day after Baseline(V1)	Grade	Causal relationship	MedDRA PT	Group
Injury, poisoning and procedural complications								
1	18	After bleeding	11/04/18	1	3-Severe	Not related to study drug	Post procedural haemorrhage	UC
Nervous system disorders								
1	32	generalisierter tonisch klinischer Anfall	14/07/19	5	3-Severe	Related to study drug	Generalised tonic-clonic seizure	UC

(🖫 Lis. 08-01-07)

Table 75: Causal relationship of adverse events to study treatment

	Group					
	IM		UC		All	
	N	PctN	N	PctN	N	PctN
Causal relationship						
Related to study drug	30	20.55	19	29.23	49	23.22
Not related to study drug	116	79.45	46	70.77	162	76.78
All	146	100.00	65	100.00	211	100.00

(🖫 Tab. 08-01-02-00b)

Table 76: Serious adverse events

	Group					
	IM		UC		All	
	N	PctN	N	PctN	N	PctN
Has the event been serious?						
Yes	12	8.22	9	13.85	21	9.95
No	134	91.78	56	86.15	190	90.05
All	146	100.00	65	100.00	211	100.00

(🖫 Tab. 08-01-02-00c)

Table 77: Overview on adverse events by MedDRA SOC

	Group					
	IM		UC		All	
	N	PctN	N	PctN	N	PctN
SOC						
Blood and lymphatic system disorders	8	5.48	3	4.62	11	5.21
Cardiac disorders	.	.	1	1.54	1	0.47
Congenital, familial and genetic disorders	.	.	1	1.54	1	0.47
Endocrine disorders	2	1.37	.	.	2	0.95
Eye disorders	1	0.68	.	.	1	0.47
Gastrointestinal disorders	17	11.64	5	7.69	22	10.43
General disorders and administration site conditions	3	2.05	2	3.08	5	2.37
Hepatobiliary disorders	1	0.68	.	.	1	0.47
Immune system disorders	11	7.53	5	7.69	16	7.58
Infections and infestations	20	13.70	11	16.92	31	14.69
Injury, poisoning and procedural complications	6	4.11	6	9.23	12	5.69
Investigations	33	22.60	8	12.31	41	19.43
Metabolism and nutrition disorders	6	4.11	3	4.62	9	4.27
Musculoskeletal and connective tissue disorders	5	3.42	.	.	5	2.37
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	1.37	.	.	2	0.95
Nervous system disorders	9	6.16	8	12.31	17	8.06
Psychiatric disorders	5	3.42	.	.	5	2.37
Renal and urinary disorders	7	4.79	5	7.69	12	5.69
Respiratory, thoracic and mediastinal disorders	2	1.37	.	.	2	0.95
Skin and subcutaneous tissue disorders	5	3.42	5	7.69	10	4.74
Vascular disorders	3	2.05	2	3.08	5	2.37
All	146	100.00	65	100.00	211	100.00

13.1.3 Analysis of Adverse Events

When considering the incidences of AEs (occurrence of AE per patient) it was found that all patients had at least one adverse event. 69% of the patients had an investigation, 54% had infections and infestations, and 43% had a gastrointestinal disorder (Table 78). Due to the small sample size no significant differences between treatment groups can be detected.

Table 78: Incidence of AE by MedDRA SOC

	Treatment N= 21	Control N= 14	Total N= 35	P
Any Adverse Event	21 (100%)	14 (100%)	35 (100%)	
Blood and lymphatic system disorders	8 (38%)	3 (21%)	11 (31%)	0.4606
Cardiac disorders	0 (0%)	1 (7%)	1 (3%)	0.4000
Congenital, familial and genetic disorders	0 (0%)	1 (7%)	1 (3%)	0.4000
Endocrine disorders	2 (10%)	0 (0%)	2 (6%)	0.5059
Eye disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Gastrointestinal disorders	11 (52%)	4 (29%)	15 (43%)	0.2958
General disorders and administration site conditions	3 (14%)	2 (14%)	5 (14%)	1.0000
Hepatobiliary disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Immune system disorders	8 (38%)	5 (36%)	13 (37%)	1.0000
Infections and infestations	12 (57%)	7 (50%)	19 (54%)	0.7391
Injury, poisoning and procedural complications	3 (14%)	5 (36%)	8 (23%)	0.2209
Investigations	16 (76%)	8 (57%)	24 (69%)	0.2831
Metabolism and nutrition disorders	5 (24%)	3 (21%)	8 (23%)	1.0000
Musculoskeletal and connective tissue disorders	5 (24%)	0 (0%)	5 (14%)	0.0689
Neoplasms benign, malignant and unspecified (incl cysts and polyp	2 (10%)	0 (0%)	2 (6%)	0.5059
Nervous system disorders	7 (33%)	7 (50%)	14 (40%)	0.4830
Psychiatric disorders	5 (24%)	0 (0%)	5 (14%)	0.0689
Renal and urinary disorders	7 (33%)	4 (29%)	11 (31%)	1.0000
Respiratory, thoracic and mediastinal disorders	2 (10%)	0 (0%)	2 (6%)	0.5059
Skin and subcutaneous tissue disorders	3 (14%)	4 (29%)	7 (20%)	0.4007
Vascular disorders	3 (14%)	2 (14%)	5 (14%)	1.0000

(🖫 Tab. 08-01-02-02a)

Table 79: Incidence of AE by MedDRA preferred term

	Treatment N= 21	Control N= 14	Total N= 35
Any Adverse Event	21 (100%)	14 (100%)	35 (100%)
Abdominal pain	1 (5%)	0 (0%)	1 (3%)
Abdominal pain upper	1 (5%)	1 (7%)	2 (6%)
Acne	1 (5%)	1 (7%)	2 (6%)
Adenoiditis	1 (5%)	0 (0%)	1 (3%)
Alopecia	1 (5%)	0 (0%)	1 (3%)
Amylase increased	1 (5%)	0 (0%)	1 (3%)

	Treatment N= 21	Control N= 14	Total N= 35
Anaemia	1 (5%)	1 (7%)	2 (6%)
Aortic aneurysm	0 (0%)	1 (7%)	1 (3%)
Arthropod bite	0 (0%)	1 (7%)	1 (3%)
BK virus infection	1 (5%)	0 (0%)	1 (3%)
Back pain	1 (5%)	0 (0%)	1 (3%)
Blood alkaline phosphatase increased	1 (5%)	0 (0%)	1 (3%)
Blood bilirubin increased	1 (5%)	0 (0%)	1 (3%)
Blood creatine phosphokinase increased	0 (0%)	1 (7%)	1 (3%)
Blood creatinine increased	3 (14%)	0 (0%)	3 (9%)
Blood glucose increased	2 (10%)	1 (7%)	3 (9%)
Blood lactate dehydrogenase increased	1 (5%)	0 (0%)	1 (3%)
Blood magnesium decreased	1 (5%)	0 (0%)	1 (3%)
Blood parathyroid hormone increased	1 (5%)	0 (0%)	1 (3%)
Blood phosphorus decreased	1 (5%)	0 (0%)	1 (3%)
Blood triglycerides increased	5 (24%)	0 (0%)	5 (14%)
Blood uric acid increased	0 (0%)	1 (7%)	1 (3%)
Body temperature increased	1 (5%)	0 (0%)	1 (3%)
C-reactive protein increased	2 (10%)	1 (7%)	3 (9%)
Candida infection	1 (5%)	0 (0%)	1 (3%)
Complications of transplanted kidney	1 (5%)	1 (7%)	2 (6%)
Constipation	1 (5%)	0 (0%)	1 (3%)
Cytomegalovirus infection	0 (0%)	1 (7%)	1 (3%)
Cytomegalovirus test positive	2 (10%)	0 (0%)	2 (6%)
Depression	2 (10%)	0 (0%)	2 (6%)
Diabetes mellitus	1 (5%)	1 (7%)	2 (6%)
Diarrhoea	6 (29%)	3 (21%)	9 (26%)
Dizziness	1 (5%)	0 (0%)	1 (3%)
Dyspepsia	1 (5%)	0 (0%)	1 (3%)
Dyspnoea	1 (5%)	0 (0%)	1 (3%)
Dyspnoea exertional	1 (5%)	0 (0%)	1 (3%)
Dysuria	1 (5%)	1 (7%)	2 (6%)
Eczema	0 (0%)	1 (7%)	1 (3%)
Encephalopathy	0 (0%)	1 (7%)	1 (3%)
Enterococcal infection	1 (5%)	0 (0%)	1 (3%)
Escherichia urinary tract infection	1 (5%)	0 (0%)	1 (3%)
Flatulence	1 (5%)	0 (0%)	1 (3%)
Fungal skin infection	0 (0%)	1 (7%)	1 (3%)
Gastric ulcer	1 (5%)	0 (0%)	1 (3%)
Gastroenteritis	1 (5%)	0 (0%)	1 (3%)
Generalised tonic-clonic seizure	0 (0%)	1 (7%)	1 (3%)
Granulocyte count decreased	0 (0%)	1 (7%)	1 (3%)
Haematoma	0 (0%)	1 (7%)	1 (3%)
Haemoglobin decreased	3 (14%)	2 (14%)	5 (14%)

	Treatment N= 21	Control N= 14	Total N= 35
Hepatic enzyme increased	1 (5%)	0 (0%)	1 (3%)
Hepatic steatosis	1 (5%)	0 (0%)	1 (3%)
Hepatitis E	0 (0%)	1 (7%)	1 (3%)
Herpes virus infection	1 (5%)	0 (0%)	1 (3%)
Hypercholesterolaemia	1 (5%)	0 (0%)	1 (3%)
Hyperhidrosis	1 (5%)	0 (0%)	1 (3%)
Hyperkalaemia	3 (14%)	0 (0%)	3 (9%)
Hyperphosphataemia	1 (5%)	0 (0%)	1 (3%)
Hypertension	2 (10%)	0 (0%)	2 (6%)
Hyperthyroidism	1 (5%)	0 (0%)	1 (3%)
Hypoaesthesia	1 (5%)	0 (0%)	1 (3%)
Hypothyroidism	1 (5%)	0 (0%)	1 (3%)
Ileus	1 (5%)	1 (7%)	2 (6%)
Impaired gastric emptying	1 (5%)	0 (0%)	1 (3%)
Infected lymphocele	1 (5%)	0 (0%)	1 (3%)
Influenza	1 (5%)	1 (7%)	2 (6%)
Insomnia	3 (14%)	0 (0%)	3 (9%)
Interleukin level increased	1 (5%)	0 (0%)	1 (3%)
Intervertebral disc protrusion	1 (5%)	0 (0%)	1 (3%)
Iron deficiency anaemia	1 (5%)	0 (0%)	1 (3%)
Kidney transplant rejection	8 (38%)	4 (29%)	12 (34%)
Lacrimation increased	1 (5%)	0 (0%)	1 (3%)
Leukocytosis	2 (10%)	0 (0%)	2 (6%)
Leukopenia	3 (14%)	2 (14%)	5 (14%)
Leukoplakia oral	1 (5%)	0 (0%)	1 (3%)
Lymphocyte count decreased	0 (0%)	1 (7%)	1 (3%)
Metabolic acidosis	0 (0%)	1 (7%)	1 (3%)
Mitochondrial enzyme deficiency	0 (0%)	1 (7%)	1 (3%)
Muscle fatigue	1 (5%)	0 (0%)	1 (3%)
Nasopharyngitis	3 (14%)	3 (21%)	6 (17%)
Nephritis	1 (5%)	0 (0%)	1 (3%)
Night sweats	1 (5%)	1 (7%)	2 (6%)
Nocturia	0 (0%)	1 (7%)	1 (3%)
Normochromic normocytic anaemia	1 (5%)	0 (0%)	1 (3%)
Oedema	2 (10%)	1 (7%)	3 (9%)
Oedema peripheral	0 (0%)	1 (7%)	1 (3%)
Oliguria	0 (0%)	1 (7%)	1 (3%)
Pain	1 (5%)	0 (0%)	1 (3%)
Paraesthesia	1 (5%)	1 (7%)	2 (6%)
Pelvic venous thrombosis	1 (5%)	0 (0%)	1 (3%)
Platelet count decreased	1 (5%)	0 (0%)	1 (3%)
Post procedural haemorrhage	0 (0%)	1 (7%)	1 (3%)
Prerenal failure	0 (0%)	1 (7%)	1 (3%)

	Treatment N= 21	Control N= 14	Total N= 35
Proteinuria	3 (14%)	0 (0%)	3 (9%)
Pruritus	0 (0%)	1 (7%)	1 (3%)
Renal adenoma	1 (5%)	0 (0%)	1 (3%)
Renal artery stenosis	1 (5%)	0 (0%)	1 (3%)
Renal graft infection	1 (5%)	1 (7%)	2 (6%)
Renal lymphocele	3 (14%)	2 (14%)	5 (14%)
Respiratory tract infection	1 (5%)	0 (0%)	1 (3%)
Rhabdomyolysis	1 (5%)	0 (0%)	1 (3%)
Scar pain	0 (0%)	1 (7%)	1 (3%)
Sinusitis	1 (5%)	0 (0%)	1 (3%)
Skin cancer	1 (5%)	0 (0%)	1 (3%)
Skin lesion	1 (5%)	0 (0%)	1 (3%)
Subileus	1 (5%)	0 (0%)	1 (3%)
Tachycardia	0 (0%)	1 (7%)	1 (3%)
Transplant rejection	0 (0%)	1 (7%)	1 (3%)
Tremor	6 (29%)	5 (36%)	11 (31%)
Tubulointerstitial nephritis	1 (5%)	1 (7%)	2 (6%)
Upper respiratory tract infection	1 (5%)	0 (0%)	1 (3%)
Urinary tract infection	1 (5%)	2 (14%)	3 (9%)
Urinary tract infection bacterial	1 (5%)	0 (0%)	1 (3%)
Vitamin D deficiency	0 (0%)	1 (7%)	1 (3%)
Vomiting	1 (5%)	0 (0%)	1 (3%)
Weight bearing difficulty	1 (5%)	0 (0%)	1 (3%)
White blood cell count decreased	2 (10%)	0 (0%)	2 (6%)
White blood cell count increased	3 (14%)	0 (0%)	3 (9%)
Wound complication	0 (0%)	1 (7%)	1 (3%)

(🖫 Tab. 08-01-02-05a)

The following table shows classification and the maximum intensity of adverse events per patient by treatment groups (Table 80).

Table 80: Adverse events per patient with max. severity

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Any Event	21 (100%)	14 (100%)	35 (100%)
Mild	4 (19%)	1 (7%)	5 (14%)
Moderate	17 (81%)	11 (79%)	28 (80%)
Severe	0 (0%)	2 (14%)	2 (6%)
Blood and lymphatic system	8 (38%)	3 (21%)	11 (31%)
Mild	8 (38%)	3 (21%)	11 (31%)
Anaemia	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Iron deficiency anaemi	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Leukocytosis	2 (10%)	0 (0%)	2 (6%)
Mild	2 (10%)	0 (0%)	2 (6%)
Leukopenia	3 (14%)	2 (14%)	5 (14%)
Mild	3 (14%)	2 (14%)	5 (14%)
Normochromic normocyti	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Cardiac disorders	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Tachycardia	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Congenital, familial and g	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Mitochondrial enzyme d	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Endocrine disorders	2 (10%)	0 (0%)	2 (6%)
Mild	2 (10%)	0 (0%)	2 (6%)
Hyperthyroidism	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Hypothyroidism	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Eye disorders	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Lacrimation increased	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Gastrointestinal disorders	11 (52%)	4 (29%)	15 (43%)
Mild	7 (33%)	3 (21%)	10 (29%)
Moderate	4 (19%)	1 (7%)	5 (14%)
Abdominal pain	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Abdominal pain upper	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Constipation	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Diarrhoea	6 (29%)	3 (21%)	9 (26%)
Mild	3 (14%)	3 (21%)	6 (17%)
Moderate	3 (14%)	0 (0%)	3 (9%)
Dyspepsia	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Flatulence	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Gastric ulcer	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Ileus	1 (5%)	1 (7%)	2 (6%)
Moderate	1 (5%)	1 (7%)	2 (6%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Impaired gastric empty	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Leukoplakia oral	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Subileus	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Vomiting	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
General disorders and admi	3 (14%)	2 (14%)	5 (14%)
Mild	0 (0%)	2 (14%)	2 (6%)
Moderate	3 (14%)	0 (0%)	3 (9%)
Oedema	2 (10%)	1 (7%)	3 (9%)
Mild	0 (0%)	1 (7%)	1 (3%)
Moderate	2 (10%)	0 (0%)	2 (6%)
Oedema peripheral	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Pain	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Hepatobiliary disorders	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Hepatic steatosis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Immune system disorders	8 (38%)	5 (36%)	13 (37%)
Mild	2 (10%)	2 (14%)	4 (11%)
Moderate	6 (29%)	3 (21%)	9 (26%)
Kidney transplant reje	8 (38%)	4 (29%)	12 (34%)
Mild	2 (10%)	2 (14%)	4 (11%)
Moderate	6 (29%)	2 (14%)	8 (23%)
Transplant rejection	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Infections and infestation	12 (57%)	7 (50%)	19 (54%)
Mild	6 (29%)	5 (36%)	11 (31%)
Moderate	6 (29%)	2 (14%)	8 (23%)
Adenoiditis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
BK virus infection	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Candida infection	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Cytomegalovirus infect	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Enterococcal infection	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Escherichia urinary tr	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Fungal skin infection	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Gastroenteritis	1 (5%)	0 (0%)	1 (3%)

Class 1 / Class 2 / Severity	IM N= 21	UC N= 14	Overall N= 35
Moderate	1 (5%)	0 (0%)	1 (3%)
Hepatitis E	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Herpes virus infection	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Infected lymphocele	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Influenza	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Nasopharyngitis	3 (14%)	3 (21%)	6 (17%)
Mild	3 (14%)	3 (21%)	6 (17%)
Renal graft infection	1 (5%)	1 (7%)	2 (6%)
Moderate	1 (5%)	1 (7%)	2 (6%)
Respiratory tract infe	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Sinusitis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Upper respiratory trac	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Infections and infestations (Continued)			
Urinary tract infectio	1 (5%)	2 (14%)	3 (9%)
Mild	1 (5%)	2 (14%)	3 (9%)
Urinary tract infectio	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Injury, poisoning and proc	3 (14%)	5 (36%)	8 (23%)
Mild	0 (0%)	1 (7%)	1 (3%)
Moderate	3 (14%)	3 (21%)	6 (17%)
Severe	0 (0%)	1 (7%)	1 (3%)
Arthropod bite	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Complications of trans	1 (5%)	1 (7%)	2 (6%)
Moderate	1 (5%)	1 (7%)	2 (6%)
Post procedural haemor	0 (0%)	1 (7%)	1 (3%)
Severe	0 (0%)	1 (7%)	1 (3%)
Renal lymphocele	3 (14%)	2 (14%)	5 (14%)
Moderate	3 (14%)	2 (14%)	5 (14%)
Wound complication	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Investigations	16 (76%)	8 (57%)	24 (69%)
Mild	13 (62%)	6 (43%)	19 (54%)
Moderate	3 (14%)	2 (14%)	5 (14%)
Amylase increased	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood alkaline phospha	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood bilirubin increa	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Blood creatine phospho	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Blood creatinine incre	3 (14%)	0 (0%)	3 (9%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	2 (10%)	0 (0%)	2 (6%)
Blood glucose increase	2 (10%)	1 (7%)	3 (9%)
Mild	2 (10%)	1 (7%)	3 (9%)
Blood lactate dehydrog	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood magnesium decrea	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood parathyroid horm	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood phosphorus decre	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood triglycerides in	5 (24%)	0 (0%)	5 (14%)
Mild	5 (24%)	0 (0%)	5 (14%)
Blood uric acid increa	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Body temperature incre	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
C-reactive protein inc	2 (10%)	1 (7%)	3 (9%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	1 (7%)	2 (6%)
Cytomegalovirus test p	2 (10%)	0 (0%)	2 (6%)
Mild	2 (10%)	0 (0%)	2 (6%)
Granulocyte count decr	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Haemoglobin decreased	3 (14%)	2 (14%)	5 (14%)
Mild	2 (10%)	2 (14%)	4 (11%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Hepatic enzyme increas	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Interleukin level incr	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Lymphocyte count decre	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Platelet count decreas	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
White blood cell count	2 (10%)	0 (0%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
White blood cell count	3 (14%)	0 (0%)	3 (9%)
Mild	3 (14%)	0 (0%)	3 (9%)
Metabolism and nutrition d	5 (24%)	3 (21%)	8 (23%)
Mild	3 (14%)	1 (7%)	4 (11%)
Moderate	2 (10%)	2 (14%)	4 (11%)
Diabetes mellitus	1 (5%)	1 (7%)	2 (6%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Mild	0 (0%)	1 (7%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Hypercholesterolaemia	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Hyperkalaemia	3 (14%)	0 (0%)	3 (9%)
Mild	2 (10%)	0 (0%)	2 (6%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Hyperphosphataemia	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Metabolic acidosis	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Vitamin D deficiency	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Musculoskeletal and connec	5 (24%)	0 (0%)	5 (14%)
Mild	2 (10%)	0 (0%)	2 (6%)
Moderate	3 (14%)	0 (0%)	3 (9%)
Back pain	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Intervertebral disc pr	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Muscle fatigue	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Rhabdomyolysis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Weight bearing difficu	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Neoplasms benign, malignan	2 (10%)	0 (0%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Renal adenoma	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Skin cancer	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Nervous system disorders	7 (33%)	7 (50%)	14 (40%)
Mild	6 (29%)	6 (43%)	12 (34%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Severe	0 (0%)	1 (7%)	1 (3%)
Dizziness	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Encephalopathy	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Generalised tonic-clon	0 (0%)	1 (7%)	1 (3%)
Severe	0 (0%)	1 (7%)	1 (3%)
Hypoaesthesia	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Paraesthesia	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)

Nervous system disorders (Continued)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Tremor	6 (29%)	5 (36%)	11 (31%)
Mild	5 (24%)	5 (36%)	10 (29%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Psychiatric disorders	5 (24%)	0 (0%)	5 (14%)
Mild	4 (19%)	0 (0%)	4 (11%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Depression	2 (10%)	0 (0%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Insomnia	3 (14%)	0 (0%)	3 (9%)
Mild	3 (14%)	0 (0%)	3 (9%)
Renal and urinary disorder	7 (33%)	4 (29%)	11 (31%)
Mild	6 (29%)	2 (14%)	8 (23%)
Moderate	1 (5%)	2 (14%)	3 (9%)
Dysuria	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Nephritis	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Nocturia	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Oliguria	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Prerenal failure	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Proteinuria	3 (14%)	0 (0%)	3 (9%)
Mild	3 (14%)	0 (0%)	3 (9%)
Renal artery stenosis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Tubulointerstitial nep	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Respiratory, thoracic and	2 (10%)	0 (0%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Dyspnoea	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Dyspnoea exertional	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Skin and subcutaneous tiss	3 (14%)	4 (29%)	7 (20%)
Mild	3 (14%)	4 (29%)	7 (20%)
Acne	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Alopecia	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Eczema	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Hyperhidrosis	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Night sweats	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Pruritus	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Scar pain	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Skin lesion	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Vascular disorders	3 (14%)	2 (14%)	5 (14%)
Mild	0 (0%)	1 (7%)	1 (3%)
Moderate	3 (14%)	1 (7%)	4 (11%)
Aortic aneurysm	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Haematoma	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Hypertension	2 (10%)	0 (0%)	2 (6%)
Moderate	2 (10%)	0 (0%)	2 (6%)
Pelvic venous thrombos	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)

(🖫 Tab. 08-01-02-12)

13.1.3.1. Treatment Related Adverse Events

During the study adverse events were rated by the investigator as possibly related to study treatments or not related. The following tables show all adverse events with a plausible relationship to study treatment.

Overall, 27 patients (77%) had at least one treatment related adverse event, 17 (81%) in the IM group and 10 (71%) in the UC group. Most AE are from the SOC Infections and infestations (37%), followed by nervous system disorders (29%) and Investigations (23%) (Table 81.) On the preferred term level most AE occur only once. Exception is tremor (N=9), nasopharyngitis (N=4), and influenza, leukopenia, and WBC decreases with N=2 each (Table 82).

Due to the overall low numbers of treatment related AE no significant differences were observed.

Table 83 shows classification and the maximum intensity of adverse events per patient by treatment groups.

Table 81: Incidence of treatment related AE by MedDRA SOC

	Treatment N= 21	Control N= 14	Total N= 35	P
Any Adverse Event	17 (81%)	10 (71%)	27 (77%)	
Blood and lymphatic system disorders	1 (5%)	1 (7%)	2 (6%)	1.0000
Congenital, familial and genetic disorders	0 (0%)	1 (7%)	1 (3%)	0.4000

	Treatment N= 21	Control N= 14	Total N= 35	P
Gastrointestinal disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Immune system disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Infections and infestations	9 (43%)	4 (29%)	13 (37%)	0.4875
Injury, poisoning and procedural complications	0 (0%)	1 (7%)	1 (3%)	0.4000
Investigations	7 (33%)	1 (7%)	8 (23%)	0.1078
Metabolism and nutrition disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Musculoskeletal and connective tissue disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Neoplasms benign, malignant and unspecified (incl cysts and polyp	1 (5%)	0 (0%)	1 (3%)	1.0000
Nervous system disorders	4 (19%)	6 (43%)	10 (29%)	0.1508
Renal and urinary disorders	0 (0%)	1 (7%)	1 (3%)	0.4000
Skin and subcutaneous tissue disorders	0 (0%)	1 (7%)	1 (3%)	0.4000

(🖫 Tab. 08-01-03-02a,b)

Table 82: Incidence of treatment related AE by MedDRA preferred term

	Treatment N= 21	Control N= 14	Total N= 35
Any Adverse Event	17 (81%)	10 (71%)	27 (77%)
Blood bilirubin increased	1 (5%)	0 (0%)	1 (3%)
Blood glucose increased	1 (5%)	0 (0%)	1 (3%)
Blood triglycerides increased	1 (5%)	0 (0%)	1 (3%)
Body temperature increased	1 (5%)	0 (0%)	1 (3%)
C-reactive protein increased	1 (5%)	0 (0%)	1 (3%)
Complications of transplanted kidney	0 (0%)	1 (7%)	1 (3%)
Cytomegalovirus test positive	1 (5%)	0 (0%)	1 (3%)
Diabetes mellitus	1 (5%)	0 (0%)	1 (3%)
Diarrhoea	1 (5%)	0 (0%)	1 (3%)
Enterococcal infection	1 (5%)	0 (0%)	1 (3%)
Escherichia urinary tract infection	1 (5%)	0 (0%)	1 (3%)
Fungal skin infection	0 (0%)	1 (7%)	1 (3%)
Gastroenteritis	1 (5%)	0 (0%)	1 (3%)
Generalised tonic-clonic seizure	0 (0%)	1 (7%)	1 (3%)
Hepatitis E	0 (0%)	1 (7%)	1 (3%)
Herpes virus infection	1 (5%)	0 (0%)	1 (3%)
Infected lymphocele	1 (5%)	0 (0%)	1 (3%)
Influenza	1 (5%)	1 (7%)	2 (6%)
Kidney transplant rejection	1 (5%)	0 (0%)	1 (3%)
Leukopenia	1 (5%)	1 (7%)	2 (6%)
Lymphocyte count decreased	0 (0%)	1 (7%)	1 (3%)
Mitochondrial enzyme deficiency	0 (0%)	1 (7%)	1 (3%)
Nasopharyngitis	2 (10%)	2 (14%)	4 (11%)
Pruritus	0 (0%)	1 (7%)	1 (3%)

	Treatment N= 21	Control N= 14	Total N= 35
Renal graft infection	1 (5%)	1 (7%)	2 (6%)
Respiratory tract infection	1 (5%)	0 (0%)	1 (3%)
Rhabdomyolysis	1 (5%)	0 (0%)	1 (3%)
Skin cancer	1 (5%)	0 (0%)	1 (3%)
Tremor	4 (19%)	5 (36%)	9 (26%)
Tubulointerstitial nephritis	0 (0%)	1 (7%)	1 (3%)
Upper respiratory tract infection	1 (5%)	0 (0%)	1 (3%)
White blood cell count decreased	2 (10%)	0 (0%)	2 (6%)

(🖫 Tab. 08-01-03-04a)

Table 83: Treatment related adverse events per patient with max. severity

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Any Event	17 (81%)	10 (71%)	27 (77%)
Mild	9 (43%)	4 (29%)	13 (37%)
Moderate	8 (38%)	5 (36%)	13 (37%)
Severe	0 (0%)	1 (7%)	1 (3%)
Blood and lymphatic system	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Leukopenia	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Congenital, familial and g	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Mitochondrial enzyme d	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Gastrointestinal disorders	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Diarrhoea	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Immune system disorders	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Kidney transplant reje	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Infections and infestation	9 (43%)	4 (29%)	13 (37%)
Mild	5 (24%)	2 (14%)	7 (20%)
Moderate	4 (19%)	2 (14%)	6 (17%)
Enterococcal infection	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Escherichia urinary tr	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Fungal skin infection	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Gastroenteritis	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Hepatitis E	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Herpes virus infection	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Infected lymphocele	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Influenza	1 (5%)	1 (7%)	2 (6%)
Mild	1 (5%)	1 (7%)	2 (6%)
Nasopharyngitis	2 (10%)	2 (14%)	4 (11%)
Mild	2 (10%)	2 (14%)	4 (11%)
Renal graft infection	1 (5%)	1 (7%)	2 (6%)
Moderate	1 (5%)	1 (7%)	2 (6%)
Respiratory tract infe	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Upper respiratory trac	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Injury, poisoning and proc	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Complications of trans	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Investigations	7 (33%)	1 (7%)	8 (23%)
Mild	5 (24%)	1 (7%)	6 (17%)
Moderate	2 (10%)	0 (0%)	2 (6%)
Blood bilirubin increa	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood glucose increase	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Blood triglycerides in	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Body temperature incre	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
C-reactive protein inc	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Cytomegalovirus test p	1 (5%)	0 (0%)	1 (3%)
Mild	1 (5%)	0 (0%)	1 (3%)
Lymphocyte count decre	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
White blood cell count	2 (10%)	0 (0%)	2 (6%)
Mild	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Metabolism and nutrition d	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Diabetes mellitus	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Musculoskeletal and connec	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Rhabdomyolysis	1 (5%)	0 (0%)	1 (3%)

Class 1 Class 2 Severity	IM N= 21	UC N= 14	Overall N= 35
Moderate	1 (5%)	0 (0%)	1 (3%)
Neoplasms benign, malignan	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Skin cancer	1 (5%)	0 (0%)	1 (3%)
Moderate	1 (5%)	0 (0%)	1 (3%)
Nervous system disorders	4 (19%)	6 (43%)	10 (29%)
Mild	4 (19%)	5 (36%)	9 (26%)
Severe	0 (0%)	1 (7%)	1 (3%)
Generalised tonic-clon	0 (0%)	1 (7%)	1 (3%)
Severe	0 (0%)	1 (7%)	1 (3%)
Tremor	4 (19%)	5 (36%)	9 (26%)
Mild	4 (19%)	5 (36%)	9 (26%)
Renal and urinary disorder	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Tubulointerstitial nep	0 (0%)	1 (7%)	1 (3%)
Moderate	0 (0%)	1 (7%)	1 (3%)
Skin and subcutaneous tiss	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)
Pruritus	0 (0%)	1 (7%)	1 (3%)
Mild	0 (0%)	1 (7%)	1 (3%)

(🖫 Tab. 08-01-03-04a)

13.1.3.2. Discontinuations of Study Treatment and Dose Modifications Due to Adverse Events

A total of 14 AE has been reported with treatment modification, 9 in the immune monitored group an 5 in the unguided control group (Table 84). 12 of the events were reported as dose modifications and 2 led to discontinuation of study treatment (listed in Table 85) and switch to another treatment regimen (listed in Table 86).

Table 84: Summary of adverse events with treatment modifications

	Group					
	IM		UC		All	
	N	PctN	N	PctN	N	PctN
Treatment modification						
No	137	93.84	60	92.31	197	93.36
Yes	9	6.16	5	7.69	14	6.64
All	146	100.00	65	100.00	211	100.00

(🖫 Tab. 08-01-02-15)

Table 85: Listing of AE which led to dose modifications

Site-Id	Pat-ID	lltName	Day after Baseline(V1)	Grade	Causal relationship	AE Treatment	Outcome	Has the event been serious?	Group
1	6	Leucopenia	98	Mild	Related to study drug	No	recovered/resolved	No	UC
1	7	Diarrhea	85	Moderate	Related to study drug	No	recovered/resolved	No	IM
1	11	Leucopenia	183	Mild	Not related to study drug	No	recovered/resolved	No	IM
1	12	White blood cell count decreased	98	Mild	Related to study drug	No	recovered/resolved	No	IM
1	13	Bilirubin increased	129	Mild	Related to study drug	No	recovered/resolved	No	IM
1	15	Kidney graft dysfunction	191	Moderate	Related to study drug	No	recovered/resolved	No	UC
1	21	BK virus infection	90	Moderate	Not related to study drug	Yes	recovered/resolved	No	IM
1	22	Tremor	29	Mild	Related to study drug	No	recovered/resolved	No	IM
1	23	CMV infection	189	Mild	Not related to study drug	Yes	recovered/resolved	No	UC
1	24	Leucopenia	87	Mild	Related to study drug	No	unknown	No	IM
1	33	Tremor	44	Mild	Related to study drug	No	recovered/resolved	No	UC
1	34	White blood cell count decreased	28	Moderate	Related to study drug	Yes	not recovered/not resolved	No	IM

(🖫 Tab. 08-01-02-16)

Table 86: List of AE which led to withdrawal of study product

Site-Id	Pat-ID	lltName	Day after Baseline(V1)	Grade	Causal relationship	AE Treatment	Outcome	Has the event been serious?	Group
1	18	Mitochondrial enzyme deficiency	20	Moderate	Related to study drug	Yes	recovered/resolved	No	UC
1	20	Kidney transplant rejection	59	Moderate	Related to study drug	Yes	recovering/resolving	No	IM

(🖫 Tab. 08-01-02-17)

13.1.4 Listing of Adverse Events by Patients

The information on adverse events was assessed in the CRF and afterwards encoded according to the MedDRA dictionary (Version 19.1).

The listing of adverse events by patient with complete information on each adverse event together with coding information is depicted in the Appendix.

13.2 Deaths and Other Serious Adverse Events

None of the patients died during the study, but a total of 21 serious adverse events have been reported, 12 in the immune monitored group and 9 in the unguided control group (Table 87). Considering causal relationship to study treatment shows that only 7 SAE were regarded to have a causal relationship to the study drug by the investigator and all come form the infections and infestations SOC (Table 88). They are shown with their MedDRA PT in Table 89.

On a per patient basis 13 patients had at least one SAE, 7 in the IM group and 6 in the UC group (Table 90). Most of the SAE fall into the SOCs infections and infestations and injury, poisoning and procedural complications, followed by gastrointestinal disorders.

Table 87: Serious adverse events by MedDRA SOC and severity

		Group					
		IM		UC		All	
		N	PctN	N	PctN	N	PctN
System Organ Class	Grade						
Gastrointestinal disorders	Moderate	2	16.67	1	11.11	3	14.29
Infections and infestations	Mild	.	.	1	11.11	1	4.76
	Moderate	5	41.67	2	22.22	7	33.33
Injury, poisoning and procedural complications	Moderate	3	25.00	2	22.22	5	23.81
	Severe	.	.	1	11.11	1	4.76
Investigations	Mild	.	.	1	11.11	1	4.76
Renal and urinary disorders	Moderate	1	8.33	.	.	1	4.76
Respiratory, thoracic and mediastinal disorders	Moderate	1	8.33	.	.	1	4.76
Vascular disorders	Moderate	.	.	1	11.11	1	4.76
All		12	100.00	9	100.00	21	100.00

(🖫 Tab. 08-01-04-01)

Table 88: Causal relationships of SAE by MedDRA SOC

	Causal relationship					
	Related to study drug		Not related to study drug		All	
	N	PctN	N	PctN	N	PctN
SOC						
Gastrointestinal disorders	.	.	3	100.00	3	100.00

	Causal relationship					
	Related to study drug		Not related to study drug		All	
	N	PctN	N	PctN	N	PctN
Infections and infestations	7	100.00	1	100.00	8	100.00
Injury, poisoning and procedural complications	.	.	6	100.00	6	100.00
Investigations	.	.	1	100.00	1	100.00
Renal and urinary disorders	.	.	1	100.00	1	100.00
Respiratory, thoracic and mediastinal disorders	.	.	1	100.00	1	100.00
Vascular disorders	.	.	1	100.00	1	100.00
All	7	100.00	14	100.00	21	100.00

(🖫 Tab. 08-01-04-05)

Table 89: Serious adverse reactions with severity by MedDRA preferred terms

		Group					
		IM		UC		All	
		N	PctN	N	PctN	N	PctN
Preferred Term	Grade						
Escherichia urinary tract infection	Moderate	1	25.00	.	.	1	14.29
Infected lymphocele	Moderate	1	25.00	.	.	1	14.29
Influenza	Mild	.	.	1	33.33	1	14.29
Renal graft infection	Moderate	1	25.00	2	66.67	3	42.86
Upper respiratory tract infection	Moderate	1	25.00	.	.	1	14.29
All		4	100.00	3	100.00	7	100.00

(🖫 Tab. 08-01-04-10)

Table 90: Incidence of SAE by MedDRA SOC

	Treatment N= 21	Control N= 14	Total N= 35	P
Any Adverse Event	7 (33%)	6 (43%)	13 (37%)	
Gastrointestinal disorders	2 (10%)	1 (7%)	3 (9%)	1.0000
Infections and infestations	3 (14%)	1 (7%)	4 (11%)	0.6350
Injury, poisoning and procedural complications	2 (10%)	2 (14%)	4 (11%)	1.0000
Investigations	0 (0%)	1 (7%)	1 (3%)	0.4000
Renal and urinary disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Respiratory, thoracic and mediastinal disorders	1 (5%)	0 (0%)	1 (3%)	1.0000
Vascular disorders	0 (0%)	1 (7%)	1 (3%)	0.4000

(🖫 Tab. 08-01-04-02a,b)

13.2.1 Listing of Deaths and Other Serious Adverse Events

During this study, no deaths were reported. The 21 SAE that were reported during the study are listed in Table 91 with the original term and the MedDRA coded preferred term (PT).

Table 91: Listing of all serious adverse events

Site-Id	Pat-ID	AE Term	Day after Baseline(V1)	Grade	Causal relationship	MedDRA PT	Group
1	3	unklarer CK und Myoglobinanstieg	365	1-Mild	Not related to study drug	Blood creatine phosphokinase i	UC
1	5	Dyspnoe	15	2-Moderate	Not related to study drug	Dyspnoea	IM
1	9	Aorten OP Neuperlach	184	2-Moderate	Not related to study drug	Aortic aneurysm	UC
1	18	After bleeding	1	3-Severe	Not related to study drug	Post procedural haemorrhage	UC
1	18	Lymphocele	15	2-Moderate	Not related to study drug	Renal lymphocele	UC
1	19	Bridenilieus	288	2-Moderate	Not related to study drug	Ileus	UC
1	20	stenosis graft atery	8	2-Moderate	Not related to study drug	Renal artery stenosis	IM
1	21	fieberhafter Infekt der oberen Atemwege	143	2-Moderate	Related to study drug	Upper respiratory tract infection	IM
1	23	Lymphocele	57	2-Moderate	Not related to study drug	Renal lymphocele	UC
1	24	NW Magenulzera (Forrest III)	15	2-Moderate	Not related to study drug	Gastric ulcer	IM
1	28	Influenza A	14	1-Mild	Related to study drug	Influenza	UC
1	28	Transplantat Pyelonephritis	115	2-Moderate	Related to study drug	Renal graft infection	UC
1	28	Pyelonephritis unter Immunsuppression Au	142	2-Moderate	Related to study drug	Renal graft infection	UC
1	30	HWI mit E.coli; Tx Verschlechterung	155	2-Moderate	Related to study drug	Escherichia urinary tract infection	IM
1	31	Lymphocele	16	2-Moderate	Not related to study drug	Renal lymphocele	IM
1	34	Minderperfusion der Transplantatniere	1	2-Moderate	Not related to study drug	Complications of transplanted	IM
1	34	Lymphocele links	43	2-Moderate	Not related to study drug	Renal lymphocele	IM
1	34	infizierte Lymphocele	71	2-Moderate	Not related to study drug	Infected lymphocele	IM
1	34	Ileus bei a.e. abdominiellen Adhäsionen	98	2-Moderate	Not related to study drug	Ileus	IM

Site-Id	Pat-ID	AE Term	Day after Baseline(V1)	Grade	Causal relationship	MedDRA PT	Group
1	34	Kreatininanstieg auf 4.3 mg/dl; Biospie:	241	2-Moderate	Related to study drug	Renal graft infection	IM
1	34	superinfizierte Lymphozele	371	2-Moderate	Related to study drug	Infected lymphocele	IM

(🖫 Lis. 08-01-08)

13.2.2 Narratives of Serious Adverse Events

Case: 453002 (Pat. 01-005): Dyspnoea

A 59 year old male patient was admitted 15 days after initiation of immunosuppression away. Dyspnoea and leukocytosis of unknown cause with suspected pulmonary hyperhydration hospitalized. At the time of admission, the daily dose was 7 mg Advagraf® p.o. With treatment with torasemide, the patient was recovered after 2 days. There is no evidence that the event was related to study therapy.

Case: 453003 (Pat. 01-003): Creatine kinase increased

A 24-year-old male patient showed elevated CK and myoglobin levels at follow-up 12 months after kidney transplantation and start of Advagraf® treatment. The Advagraf® dose was 8 mg/d p.o. Further, the patient took 1440 mg Myfortic and 2.5 mg prednisolone. The patient was hospitalized and forced diuresis was initiated. During the stay, the values improved, and he could be discharged 4 days later. Immunosuppression was continued unchanged. In retrospect, the event was probably caused by excessive weight training. There is no association with study therapy.

Case: 453004 (Pat. 01-018): Postoperative haemorrhage

A 21-year-old male patient presented with a splash haemorrhage from the rectus abdominis muscle on the same day of transplantation and 1 day after initiation with sustained-release tacrolimus. Immediate revision surgery was successful. At the time of the event, the patient was receiving Envarsus (5 mg/d), Myfortic (1440 mg/d), and SDH (125 mg/d). Advagraf was then switched permanently 5 days later. The reason for the event is thought to be a tearing cough. A possible association with study therapy is denied by the investigator and sponsor.

Case: 453005 (Pat. 01-018): Lymphocele

A 21-year-old male patient developed a lymphocele 14 days after kidney transplantation. One day after transplantation, a revision had already been required away. of a post-transplant haemorrhage. At the time of the event, the patient was receiving immunosuppressive therapy with Advagraf (14 mg/d), Myfortic (1440 mg/d), and prednisolone (20 mg/d). Fenestration of the lymphocele resulted in improvement. There is no correlation with the study medication.

Case: 453006 (Pat. 01-020): Stenosis of the transplant artery

A 33-year-old male patient showed decreased excretion 7 days after renal transplantation. The patient was receiving immunosuppressive therapy with Prograf (14 mg/d) and Myfortic (1440 mg/d) at the time. The patient had received Advagraf (13 mg/d) for the first 6 days and was then switched to Prograf. The stenosis of the graft artery was repaired by vascular grafting. At 19 days, the patient was discharged as recovered. Immunosuppressive therapy was continued unchanged. A possible association with the study medication is denied.

Case: 453007 (Pat. 01-023): Lymphocele

A 27-year-old male patient was hospitalized with a lymphocele 56 days after initiation of Advagraf therapy. Concomitant creatinine elevation was noted. His immunosuppressive therapy included Myfortic (1440 mg/d) and Decortin (5 mg/d) in addition to Advagraf (7 mg/d). A drain placed to treat the lymphocele later had to be sutured over because of bleeding from the insertion site. Study therapy was continued unchanged. After 14 days, the patient was discharged as recovered. A possible association with the study medication is denied.

Case 453008 (Pat. 01-024): Gastric ulcer

A 33-year-old female patient was hospitalized 14 days after renal transplantation due to Hb drop to 6.8 mg/dl and hypophosphatemia (min. 0.7 mg/dl). Study therapy was Advagraf® (12 mg/d), Myfortic (1440 mg/d) and Decortin (20 mg/d). A gastroscopy performed diagnosed a gastric ulcer. Concomitant urinary tract infection with Klebsiella pneumoniae in the urine was reported.

Use of the investigational medication was continued unchanged. After treatment with Riopan gel and Pantozol, the patient was discharged as recovered after 5 days. An association with the investigational medication is possible according to the investigator/sponsor's assessment. Gastrointestinal events of this type are described as frequent events (≥ 1/100, ≤ 1/10) in the SmPC.

Case: 453010 (Pat. 01-019): Briden's ileus

A 38-year-old female patient was hospitalized 228 days after initiation of immunosuppressive therapy (Advagraf® 5 mg/d, Myfortic 720 mg/d, prednisolone 5 mg/d) with nausea, vomiting, and impaired urine output and treated with volume replacement for 1 day and discharged. A stool examination and tests for CMV and TAC were performed. She was readmitted 4 days later with persistent vomiting and with increasing abdominal pain. CT scan revealed marked briden ileus with indication for surgery. After exploratory laparotomy, the patient was discharged as recovered after 14 days. Study therapy was continued unchanged. No association with the study medication is seen.

Case 453011 (Pat. 01-028): Influenza A

A 57-year-old male patient developed cough and fever at 38.3 oC 14 days after study initiation and immunosuppression with Envarsus®/Myfortic/Prednisolone (current dosage: Envarsus® 10 mg/d, Myfortic 1440 mg/d, Prednisolone 20 mg/d). He was initially treated with tazobac, acetaminophen and jonosteril i.v. and after influenza A detection (PCR) with Tamiflu 75 mg. After 2 days, the patient could be discharged. The investigator/sponsor confirmed a possible connection with the test medication.

Case 453012 (Pat. 01-028): Transplant Pyelonephritis

A 57-year-old male patient was admitted to the hospital with graft pyelonephritis almost 4 months after kidney transplantation and immunosuppression with Envarsus®/Myfortic/Prednisolone (current dosage: Envarsus® 2.5 mg/d, Myfortic 1440 mg/d, Prednisolone 5 mg/d). On the day of admission, CRP was 5.1 mg/dl (normal range < 0.5 mg/dl). E. faecalis was detected in the urine. The patient was treated with piperacllin/tazobactam for 4 days. After 5 days, the patient was discharged with ciprofloxacin for 10 days. An association with the investigational medication is possible.

Case 453013 (Pat. 01-31): Lymphocele

A 31-year-old male patient required surgical treatment (peritoneal fenestration) for a lymphocele 16 days after enrollment due to terminal renal failure associated with mesangioproliferative glomerulonephritis & nephrosclerosis. The patient was currently receiving immunosuppression with Envarsus® 7mg/d, Myfortic 1440 mg/d, Prednisolone 20mg/d. No therapy was given beyond that and after 6 days the patient was considered recovered. A connection with the investigational medication was considered unlikely by the treating physician and also denied by the sponsor.

Case 453014 (Pat. 01-028): Pyelonephritis

Approximately one month after initial hospitalization away. Graft pyelonephritis, the patient was readmitted with fever and chills under immunosuppression with Envarsus®/Myfortic/Prednisolone (current dosage: Envarsus® 2.5 mg/d, Myfortic 540 mg/d, Prednisolone 5 mg/d). On admission, CRP was 6.7 mg/dl and leukocytes were 21.6 G/L. A chest CT to rule out pneumonia was performed. This was followed by a diagnosis of pyelonephritis with evidence of E. faecalis in the urine. The patient received antibiotic therapy with piperacillin/tazobactam followed by Augmentan for a total of 15 days. He was discharged 7 days after admission, after which he was symptom-free. An association with the investigational medication is assessed as possible.

Both cases 453012 and 453014 are considered independent events due to the time interval and are therefore also included separately in the listings in the appendix.

Case 453015 (Pat. 01-021): Febrile upper respiratory tract infection

A 58 year old male patient was hospitalized for a febrile upper respiratory tract infection almost 5 months after transplantation and initiation of immunosuppression with Advagraf®/Myfortic/ Prednisolone (current dosage: Advagraf® 12mg/d, Myfortic 360 mg/d, , Prednisolone 5 mg/d) due to autosomal dominant inherited polycystic kidney disease (ADPKD). On the day after admission, CRP was 9.7 mg/dl. He received oral antibiotics with amoxicillin/clavulanic acid and was discharged as recovered after 5 days. A correlation with the test medication is possible.

Case 453016 (Pat. 01-034): Inferior perfusion of the transplant kidney

A 47-year-old male patient showed a lack of perfusion in duplex sonography during postoperative control after kidney transplantation and the indication for emergency revision was given. Poor venous conditions had already been noticed in the patient during transplantation. He underwent immediate surgical intervention with thrombectomy of the left renal/iliac vein, reattachment of the

anastomosis to the renal vein, and patch-plasty of the left renal vein. Afterwards, duplex sonography showed good perfusion of the kidney. After 7 days, a planned second-look surgery was performed. During this procedure, a kidney biopsy was performed with persistently high creatinine levels, which revealed a suspected minimal acute cellular transplant reaction (Banff III). The patient then received cortisone shock therapy and in the further course the retention parameters recovered. Further sonographic checks showed good perfusion. The patient was currently receiving Envarsus® 15 mg/d, Myfortic 1440 mg/d, Prednisolone 20 mg/d as an immunosuppressive regimen. Investigator and sponsor see no association with the investigational medication.

Case 453017 (Pat. 01-009): Infrarenal aortic aneurysm

The 62-year-old male patient was admitted to an out-of-hospital clinic 7 months after renal transplantation and immunosuppression with Advagraf®/Myfortic/Prednisolone (current: Advagraf® 7 mg/d, Myfortic 720 mg/d, Prednisolone 5 mg/d) for an infrarenal aortic aneurysm. An endovascular aortic repair (EVAR) was performed and subsequently, after 12 days, a lymphatic cyst in the right groin was surgically evacuated. Thereafter, the patient recovered without further complications. A connection with the study medication is not seen by the investigator and sponsor.

Case 453018 (Pat. 01-034): Lymphocele

The 47-year-old male patient was hospitalized 42 days after enrolment and immunosuppression with Envarsus®/Myfortic/Prednisolone (current: Envarsus® 6 mg/d, Myfortic 1440 mg/d, Prednisolone 20mg/d) due to a lymphocele. Surgical lymphocele evacuation was performed immediately. After 16 days, the patient was discharged as recovered. Neither investigator nor sponsor see a connection with the study medication.

Case 453019 (Pat. 01-034): Infected lymphocele

A 47-year-old male patient, after undergoing surgical revision for a lymphocele (for which no association with the study medication was seen) just 5 weeks after enrolment in the study and initiation of immunosuppression with Envarsus®/Myfortic/Prednisolone, was readmitted after another month for an infected lymphocele (current dosage: Envarsus® 5 mg/d, Myfortic 702 mg/d, Prednisolone10 mg/d). CRP on admission was 7.7 mg/dl. After renewed surgical treatment and antibiosis with meropenem for 12 days, he was discharged as recovered after 21 days. The association with the study medication was evaluated as possible.

Case 453020 (Pat. 01-034): Briden Ileus

This 47-year-old male patient was admitted 3 months after renal transplantation and immunosuppression with Envarsus®/Myfortic/Prednisolone (current: Envarsus® 10 mg/d, Myfortic 720 mg/d, Prednisolone 10 mg/d) with paraytic ileus and suspected hernia and recurrent lymphocele. On admission, the patient presented with markedly worsened general condition and persistent vomiting. With low fluid intake, his last bowel movement was 5 days ago. CRP on admission was 24.5 mg/dl. Sonographically, fluid was detected around the transplant kidney with suspicion of recurrence of the known lymphocele. Further, multiple intestinal loops and suspected hernia were detected. Small bowel segment resection and adhesiolysis were performed first, and gastroscopy with botulinus toxin injection in the pylorus was performed if gastroparesis persisted. Further, a lesion was found in the gastric corpus, which bioptically proved to be gastric mucosa free

of inflammation with marked oedema, and an axial hernia and reflux esophagitis were diagnosed. With a complicated course, the patient was discharged as recovered after 2 months. Neither the investigator nor the sponsor see any connection with the study medication.

Case 453021 (Pat. 01-030): Urinary tract infection with E. coli / graft deterioration

A 26 year old female patient was admitted to an external hospital 5 months after kidney transplantation (as a result of haemolytic uremic syndrome (HUS) after EHEC infection) and immunosuppression with Envarsus®/Myfortic/Prednisolone (current dosage: Envarsus® 5mg/d, Myfortic 1440 mg/d, Prednisolone 5 mg/d) due to deterioration of renal function (creatinine increase; 1. 4 mg/dl on admission), after outpatient treatment of a urinary tract infection with ciprofloxacin had been unsuccessful. When E. coli was detected, i.v. antibiotic treatment with ceftriaxone was administered as an inpatient. After 6 days, the patient was discharged as recovered. A connection with the test medication is considered possible.

Case 453022 (Pat. 01-034) acute suppurative transplant pyelonephritis

A 48-year-old male patient was hospitalized for pyelonephritis 8 months after renal transplantation and treatment with Envarsus®/ Myfortic/prednisolone (Envarsus® 5.5 mg/d, everolimus 1.5 mg, prednisolone 5 mg) and developed a Banff 4IA reaction 12 days later. A biopsy was performed and followed by vancomycin and prednisolone shock therapy. The patient recovered and was discharged from the hospital after 15 days. The event was considered by the investigator to be possibly related to the study medication.

Case 453023 (Pat. 01-034) Superinfected lymphocele

A 48-year-old male patient developed an infected lymphocele (right paramedian) approximately 1 year after renal transplantation and treatment with Envarsus®/ Myfortic/prednisolone (Envarsus® 5.5 mg/d, everolimus 1.5 mg, prednisolone 5 mg) and was hospitalized for diagnosis and subsequent CT-guided drainage (2 times). The patient recovered and was discharged after 11 days. The investigator assumed a causal relationship with the investigational medication.

13.3 Clinical Laboratory Evaluation

Laboratory data was analysed in the ITT population. Laboratory samples were complete at screening and during the trial. Laboratory normal ranges and updates during the study were collected for the trial site. Laboratory findings qualifying as adverse event were reported as adverse events and listed in the adverse events section.

All laboratory values were flagged as Low (L: below the lower normal) or High (H: above the upper border) and the changes displayed by shift tables. All laboratory data tables can be found in the appendix.

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

13.4.1 Vital Signs

Vital signs were recorded at all visit and will be presented in the appendix.

13.4.2 Concomitant Medication and Diseases

Prior and concomitant diseases were reported at the inclusion visit. Later onset of a concomitant disease is by definition an adverse events and will be analysed in the adverse events section.

Concomitant medications were documented throughout the study and as treatment of adverse events.

13.4.2.1. Concomitant Medication

For this analysis the medication has been classified as prior medication (stopped prior to study start) and concomitant medication (ongoing at study start). Treatments of adverse events have been reported with the AEs but are included in this section as a special category of concomitant medication. The following tables show the reported products by the ATC level 2 (therapeutic main group) for each treatment phase.

Overall 867 medications have been recorded during the study, 225 (26%) classified as previous medication and 642 (74%) classified as concomitant medication. Medications with a frequency of more than 5% of all reports were vitamins (9.9%), drug for acid related disorders (9.0%), diuretics (8.1%), other therapeutic products (7.8%), calcium channel blockers (7.4%), antihypertensives (6.6%) antianemic preparations (6.3%), and beta blocking agents (5.2%) (Table 92). Table 93 shows these data by treatment arm with no obvious differences. When comparing the mean number of medications reported also no difference is found (mean(SD)=25,5±9.1 with immune monitoring and 23.6±7.5 in the unguided control, p=0.5252) (Table 94, Figure 16).

Table 92: Prior and concomitant medications according to ATC class by category

	Type					
	Concomitant med.		Previous med.		All	
	N	PctN	N	PctN	N	PctN
ATC group						
A11: Vitamins	54	8.4	32	14.2	86	9.9
A02: Drugs for acid related disorders	68	10.6	10	4.4	78	9.0
C03: Diuretics	44	6.9	26	11.6	70	8.1
V03: All other therapeutic products	42	6.5	26	11.6	68	7.8
C08: Calcium channel blockers	48	7.5	16	7.1	64	7.4
C02: Antihypertensives	41	6.4	16	7.1	57	6.6
B03: Antianemic preparations	33	5.1	22	9.8	55	6.3
C07: Beta blocking agents	32	5.0	13	5.8	45	5.2

	Type					
	Concomitant med.		Previous med.		All	
	N	PctN	N	PctN	N	PctN
J01: Antibacterials for systemic use	41	6.4	1	0.4	42	4.8
C09: Agents acting on the renin-angiotensin system	19	3.0	18	8.0	37	4.3
J05: Antivirals for systemic use Human only	32	5.0	.	.	32	3.7
A12: Mineral supplements	17	2.6	10	4.4	27	3.1
C10: Lipid modifying agents	19	3.0	6	2.7	25	2.9
H02: Corticosteroids for systemic use	24	3.7	.	.	24	2.8
B01: Antithrombotic agents	16	2.5	4	1.8	20	2.3
M04: Antigout preparations	11	1.7	7	3.1	18	2.1
A01: Stomatological preparations	13	2.0	.	.	13	1.5
L04: Immunosuppressants	13	2.0	.	.	13	1.5
H05: Calcium homeostasis	9	1.4	4	1.8	13	1.5
A10: Drugs used in diabetes	10	1.6	.	.	10	1.2
N02: Analgesics	8	1.2	.	.	8	0.9
B05: Blood substitutes and perfusion solutions	2	0.3	2	0.9	4	0.5
A06: Laxatives	2	0.3	2	0.9	4	0.5
N05: Psycholeptics	4	0.6	.	.	4	0.5
H03: Thyroid therapy	3	0.5	1	0.4	4	0.5
V06: General nutrients	2	0.3	2	0.9	4	0.5
C05: Vasoprotectives	4	0.6	.	.	4	0.5
A03: Drugs for functional gastrointestinal disorders	4	0.6	.	.	4	0.5
G04: Urologicals	3	0.5	.	.	3	0.3
R03: Drugs for obstructive airway diseases	1	0.2	1	0.4	2	0.2
C01: Cardiac therapy	1	0.2	1	0.4	2	0.2
A07: Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	2	0.3	.	.	2	0.2
G03: Sex hormones and modulators of the genital system	2	0.3	.	.	2	0.2
N07: Other nervous system drugs	.	.	2	0.9	2	0.2
J02: Antimycotics for systemic use	2	0.3	.	.	2	0.2
N03: Antiepileptics	1	0.2	1	0.4	2	0.2
D07: Corticosteroids, dermatological preparations	2	0.3	.	.	2	0.2
N06: Psychoanaleptics	2	0.3	.	.	2	0.2
D01: Antifungals for dermatological use	2	0.3	.	.	2	0.2
A05: Bile and liver therapy	2	0.3	.	.	2	0.2
A09: Digestives, including enzymes	2	0.3	.	.	2	0.2
R06: Antihistamines for systemic use	1	0.2	1	0.4	2	0.2
Z01: Product without ATC code	1	0.2	.	.	1	0.1
N04: Anti-parkinson drugs	1	0.2	.	.	1	0.1
L03: Immunostimulants	1	0.2	.	.	1	0.1
M03: Muscle relaxants	1	0.2	.	.	1	0.1
C04: Peripheral vasodilators	.	.	1	0.4	1	0.1
All	642	100.0	225	100.0	867	100.0

(🖫 Tab. 03-02-04)

Table 93: Prior and concomitant medications by treatment arm

	Treatment					
	IM<ImmuneMonitoring>		UC<UnguidedControl>		All	
	N	PctN	N	PctN	N	PctN
ATC group						
A11: Vitamins	49	9.1	37	11.2	86	9.9
A02: Drugs for acid related disorders	47	8.8	31	9.4	78	9.0
C03: Diuretics	40	7.5	30	9.1	70	8.1
V03: All other therapeutic products	41	7.6	27	8.2	68	7.8
C08: Calcium channel blockers	41	7.6	23	6.9	64	7.4
C02: Antihypertensives	37	6.9	20	6.0	57	6.6
B03: Antianemic preparations	37	6.9	18	5.4	55	6.3
C07: Beta blocking agents	27	5.0	18	5.4	45	5.2
J01: Antibacterials for systemic use	32	6.0	10	3.0	42	4.8
C09: Agents acting on the renin-angiotensin system	24	4.5	13	3.9	37	4.3
J05: Antivirals for systemic use Human only	17	3.2	15	4.5	32	3.7
A12: Mineral supplements	20	3.7	7	2.1	27	3.1
C10: Lipid modifying agents	14	2.6	11	3.3	25	2.9
H02: Corticosteroids for systemic use	16	3.0	8	2.4	24	2.8
B01: Antithrombotic agents	10	1.9	10	3.0	20	2.3
M04: Antigout preparations	9	1.7	9	2.7	18	2.1
A01: Stomatological preparations	10	1.9	3	0.9	13	1.5
L04: Immunosuppressants	9	1.7	4	1.2	13	1.5
H05: Calcium homeostasis	10	1.9	3	0.9	13	1.5
A10: Drugs used in diabetes	7	1.3	3	0.9	10	1.2
N02: Analgesics	3	0.6	5	1.5	8	0.9
B05: Blood substitutes and perfusion solutions	.	.	4	1.2	4	0.5
A06: Laxatives	2	0.4	2	0.6	4	0.5
N05: Psycholeptics	4	0.7	.	.	4	0.5
H03: Thyroid therapy	2	0.4	2	0.6	4	0.5
V06: General nutrients	3	0.6	1	0.3	4	0.5
C05: Vasoprotectives	4	0.7	.	.	4	0.5
A03: Drugs for functional gastrointestinal disorders	4	0.7	.	.	4	0.5
G04: Urologicals	2	0.4	1	0.3	3	0.3
R03: Drugs for obstructive airway diseases	2	0.4	.	.	2	0.2
C01: Cardiac therapy	2	0.4	.	.	2	0.2
A07: Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	.	.	2	0.6	2	0.2
G03: Sex hormones and modulators of the genital system	2	0.4	.	.	2	0.2
N07: Other nervous system drugs	.	.	2	0.6	2	0.2
J02: Antimycotics for systemic use	.	.	2	0.6	2	0.2

	Treatment					
	IM<ImmuneMonitoring>		UC<UnguidedControl>		All	
	N	PctN	N	PctN	N	PctN
N03: Antiepileptics	.	.	2	0.6	2	0.2
D07: Corticosteroids, dermatological preparations	1	0.2	1	0.3	2	0.2
N06: Psychoanaleptics	2	0.4	.	.	2	0.2
D01: Antifungals for dermatological use	.	.	2	0.6	2	0.2
A05: Bile and liver therapy	.	.	2	0.6	2	0.2
A09: Digestives, including enzymes	.	.	2	0.6	2	0.2
R06: Antihistamines for systemic use	2	0.4	.	.	2	0.2
Z01: Product without ATC code	.	.	1	0.3	1	0.1
N04: Anti-parkinson drugs	1	0.2	.	.	1	0.1
L03: Immunostimulants	1	0.2	.	.	1	0.1
M03: Muscle relaxants	1	0.2	.	.	1	0.1
C04: Peripheral vasodilators	1	0.2	.	.	1	0.1
All	536	100.0	331	100.0	867	100.0

(🖫 Tab. 03-02-06)

Table 94: Mean number of medications per patient

Treatment	N	Mean	Std Dev	Std Err	Minimum	Maximum
IM<ImmuneMonitoring>	21	25.5238	9.0698	1.9792	16.0000	54.0000
UC<UnguidedControl>	14	23.6429	7.5101	2.0071	11.0000	41.0000
Diff (1-2)		1.8810	8.4897	2.9292		

P=0.5252 (TTest, equal variances)
(🖫 Tab. 03-02-01)

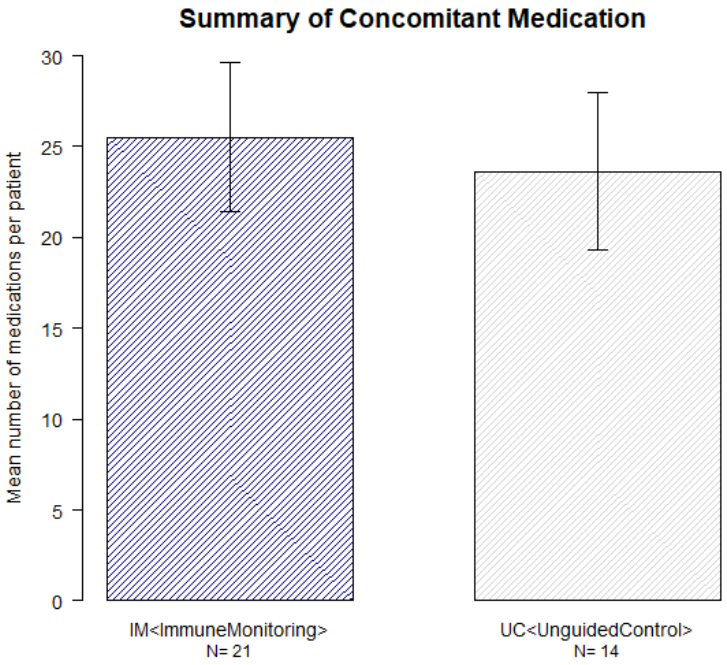

Figure 16: Mean number of medications per patient

(🖫 Tab. 03-02-02)

All patients had concomitant medication and previous medications have been reported in 94% of the patients (N=33) and 89% (N=93) have reported AE treatments with no relevant differences between treatment arms (Table 95).

Regarding the incidence (on a per patient level) of previous medications a difference can be seen in the previous use of antianemic preparations in 57% of the patients in the IM (immune monitoring) group and 21% of the patients in the UC (unguided control) group (Table 96). When comparing concomitant medications (Table 97).or treatments for AEs (Table 98) no significant difference was found on the ATC class level

A detailed list of all medications can be found in the appendix.

Table 95: Incidences of medications by category

Category	Treatment N= 21	Control N= 14	Total N= 35
Any previous medication	20 (95%)	13 (93%)	33 (94%)
Any concomitant medication	21 (100%)	14 (100%)	35 (100%)
Any AE treatment	18 (86%)	13 (93%)	31 (89%)

(🖫 Tab. 03-02-14, 16, 20)

Table 96: Incidence of previous medications at ATC class level

ATC class	Treatment N	(%)	Control N	(%)	Total N	(%)	P
A02: Drugs for acid related disorders	5	23.81	3	21.43	8	22.86	1.0000
A06: Laxatives	0	0.00	2	14.29	2	5.71	0.1529
A11: Vitamins	14	66.67	7	50.00	21	60.00	0.4830
A12: Mineral supplements	6	28.57	2	14.29	8	22.86	0.4307
B01: Antithrombotic agents	1	4.76	2	14.29	3	8.57	0.5508
B03: Antianemic preparations	12	57.14	3	21.43	15	42.86	0.0461
B05: Blood substitutes and perfusion solutions	0	0.00	1	7.14	1	2.86	0.4000
C01: Cardiac therapy	1	4.76	0	0.00	1	2.86	1.0000
C02: Antihypertensives	7	33.33	5	35.71	12	34.29	1.0000
C03: Diuretics	13	61.90	10	71.43	23	65.71	0.7210
C04: Peripheral vasodilators	1	4.76	0	0.00	1	2.86	1.0000
C07: Beta blocking agents	6	28.57	7	50.00	13	37.14	0.2882
C08: Calcium channel blockers	10	47.62	6	42.86	16	45.71	1.0000
C09: Agents acting on the renin-angiotensin system	12	57.14	5	35.71	17	48.57	0.3053
C10: Lipid modifying agents	2	9.52	4	28.57	6	17.14	0.1907
H03: Thyroid therapy	0	0.00	1	7.14	1	2.86	0.4000
H05: Calcium homeostasis	2	9.52	2	14.29	4	11.43	1.0000
J01: Antibacterials for systemic use	0	0.00	1	7.14	1	2.86	0.4000
M04: Antigout preparations	3	14.29	4	28.57	7	20.00	0.4007
N03: Antiepileptics	0	0.00	1	7.14	1	2.86	0.4000
N07: Other nervous system drugs	0	0.00	1	7.14	1	2.86	0.4000
R03: Drugs for obstructive airway diseases	1	4.76	0	0.00	1	2.86	1.0000
R06: Antihistamines for systemic use	1	4.76	0	0.00	1	2.86	1.0000
V03: All other therapeutic products	11	52.38	8	57.14	19	54.29	1.0000
V06: General nutrients	1	4.76	1	7.14	2	5.71	1.0000
Total	21	100.00	14	100.00	35	100.00	.

(🖫 Tab. 03-02-13)

Table 97: Incidence of concomitant medications at ATC class level

ATC class	Treatment N	(%)	Control N	(%)	Total N	(%)	P
A01: Stomatological preparations	7	33.33	3	21.43	10	28.57	0.7041
A02: Drugs for acid related disorders	21	100.00	14	100.00	35	100.00	.
A03: Drugs for functional gastrointestinal disorders	2	9.52	0	0.00	2	5.71	0.5059
A05: Bile and liver therapy	0	0.00	1	7.14	1	2.86	0.4000
A06: Laxatives	1	4.76	0	0.00	1	2.86	1.0000
A09: Digestives, including enzymes	0	0.00	1	7.14	1	2.86	0.4000
A10: Drugs used in diabetes	1	4.76	0	0.00	1	2.86	1.0000
A11: Vitamins	14	66.67	12	85.71	26	74.29	0.2621
A12: Mineral supplements	7	33.33	4	28.57	11	31.43	1.0000

ATC class	Treatment N	(%)	Control N	(%)	Total N	(%)	P
B01: Antithrombotic agents	7	33.33	5	35.71	12	34.29	1.0000
B03: Antianemic preparations	11	52.38	10	71.43	21	60.00	0.3109
C02: Antihypertensives	13	61.90	8	57.14	21	60.00	1.0000
C03: Diuretics	15	71.43	12	85.71	27	77.14	0.4307
C05: Vasoprotectives	2	9.52	0	0.00	2	5.71	0.5059
C07: Beta blocking agents	18	85.71	10	71.43	28	80.00	0.4007
C08: Calcium channel blockers	20	95.24	12	85.71	32	91.43	0.5508
C09: Agents acting on the renin-angiotensin system	10	47.62	6	42.86	16	45.71	1.0000
C10: Lipid modifying agents	7	33.33	5	35.71	12	34.29	1.0000
D01: Antifungals for dermatological use	0	0.00	1	7.14	1	2.86	0.4000
G03: Sex hormones and modulators of the genital system	1	4.76	0	0.00	1	2.86	1.0000
G04: Urologicals	2	9.52	1	7.14	3	8.57	1.0000
H03: Thyroid therapy	1	4.76	1	7.14	2	5.71	1.0000
H05: Calcium homeostasis	5	23.81	1	7.14	6	17.14	0.3662
J01: Antibacterials for systemic use	4	19.05	1	7.14	5	14.29	0.6272
J02: Antimycotics for systemic use	0	0.00	1	7.14	1	2.86	0.4000
J05: Antivirals for systemic use Human only	14	66.67	12	85.71	26	74.29	0.2621
L04: Immunosuppressants	1	4.76	0	0.00	1	2.86	1.0000
M04: Antigout preparations	4	19.05	3	21.43	7	20.00	1.0000
N02: Analgesics	1	4.76	1	7.14	2	5.71	1.0000
N05: Psycholeptics	1	4.76	0	0.00	1	2.86	1.0000
N06: Psychoanaleptics	1	4.76	0	0.00	1	2.86	1.0000
R03: Drugs for obstructive airway diseases	1	4.76	0	0.00	1	2.86	1.0000
V03: All other therapeutic products	20	95.24	13	92.86	33	94.29	1.0000
V06: General nutrients	2	9.52	0	0.00	2	5.71	0.5059
Z01: Product without ATC code	0	0.00	1	7.14	1	2.86	0.4000
Total	21	100.00	14	100.00	35	100.00	.

(🖫 Tab. 03-02-15)

Table 98: Incident of AE treatments at ATC class level

ATC class	Treatment N	(%)	Control N	(%)	Total N	(%)	P
A01: Stomatological preparations	2	9.52	0	0.00	2	5.71	0.5059
A02: Drugs for acid related disorders	2	9.52	1	7.14	3	8.57	1.0000
A03: Drugs for functional gastrointestinal disorders	2	9.52	0	0.00	2	5.71	0.5059
A06: Laxatives	1	4.76	0	0.00	1	2.86	1.0000
A07: Antidiarrheals, intestinal anti-inflammatory/anti-infec	0	0.00	2	14.29	2	5.71	0.1529
A10: Drugs used in diabetes	2	9.52	2	14.29	4	11.43	1.0000
A11: Vitamins	0	0.00	1	7.14	1	2.86	0.4000
A12: Mineral supplements	1	4.76	0	0.00	1	2.86	1.0000
B01: Antithrombotic agents	2	9.52	1	7.14	3	8.57	1.0000

ATC class	Treatment N	(%)	Control N	(%)	Total N	(%)	P
B03: Antianemic preparations	2	9.52	2	14.29	4	11.43	1.0000
B05: Blood substitutes and perfusion solutions	0	0.00	2	14.29	2	5.71	0.1529
C01: Cardiac therapy	1	4.76	0	0.00	1	2.86	1.0000
C03: Diuretics	2	9.52	1	7.14	3	8.57	1.0000
C05: Vasoprotectives	2	9.52	0	0.00	2	5.71	0.5059
C10: Lipid modifying agents	1	4.76	0	0.00	1	2.86	1.0000
D01: Antifungals for dermatological use	0	0.00	1	7.14	1	2.86	0.4000
D07: Corticosteroids, dermatological preparations	1	4.76	1	7.14	2	5.71	1.0000
H02: Corticosteroids for systemic use	10	47.62	7	50.00	17	48.57	1.0000
J01: Antibacterials for systemic use	7	33.33	4	28.57	11	31.43	1.0000
J02: Antimycotics for systemic use	0	0.00	1	7.14	1	2.86	0.4000
J05: Antivirals for systemic use Human only	2	9.52	3	21.43	5	14.29	0.3691
L03: Immunostimulants	1	4.76	0	0.00	1	2.86	1.0000
L04: Immunosuppressants	5	23.81	4	28.57	9	25.71	1.0000
M03: Muscle relaxants	1	4.76	0	0.00	1	2.86	1.0000
N02: Analgesics	2	9.52	2	14.29	4	11.43	1.0000
N03: Antiepileptics	0	0.00	1	7.14	1	2.86	0.4000
N04: Anti-parkinson drugs	1	4.76	0	0.00	1	2.86	1.0000
N05: Psycholeptics	3	14.29	0	0.00	3	8.57	0.2588
N06: Psychoanaleptics	1	4.76	0	0.00	1	2.86	1.0000
R06: Antihistamines for systemic use	1	4.76	0	0.00	1	2.86	1.0000
V03: All other therapeutic products	2	9.52	0	0.00	2	5.71	0.5059
Total	21	100.00	14	100.00	35	100.00	.

(🖫 Tab. 03-02-19)

13.4.2.2. Prior and Concomitant Diseases

Overall, 201 prior and concomitant diseases were reported, 37 previous diseases (ended prior to study start) and 164 concomitant diseases (ongoing during the study). Most diseases reported endocrine, nutritional and metabolic diseases followed by diseases of the circulatory system (Table 99). When comparing the treatment arms. Table 100 shows the same data by treatment arm and no suspicious differences were found. Comparing the mean number of diseases per patient was comparable between treatment arms (Table 101, Figure 17).

Comparing prior diseases on a per patient basis (Table 102) as well as concomitant diseases (Table 103) does not show any significant differences between treatment arms.

Table 99: Overview on prior/concomitant diseases by ICD-10 chapter

	Type					
	Conc.		Prior		All	
	N	PctN	N	PctN	N	PctN

	Type					
	Conc.		Prior		All	
	N	PctN	N	PctN	N	PctN
ICD-10 Chapter						
04: Endocrine, nutritional and metabolic diseases (E00-E89)	64	39.02	4	10.81	68	33.83
09: Diseases of the circulatory system (I00-I99)	40	24.39	2	5.41	42	20.90
03: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	18	10.98	3	8.11	21	10.45
11: Diseases of the digestive system (K00-K94)	7	4.27	4	10.81	11	5.47
23: Surgical and other procedures (Ext.)	4	2.44	5	13.51	9	4.48
01: Certain infectious and parasitic diseases (A00-B99)	.	.	7	18.92	7	3.48
18: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	5	3.05	1	2.70	6	2.99
06: Diseases of the nervous system (G00-G99)	4	2.44	2	5.41	6	2.99
21: Factors influencing health status and contact with health services (Z00-Z99)	4	2.44	1	2.70	5	2.49
14: Diseases of the genitourinary system (N00-N99)	4	2.44	1	2.70	5	2.49
10: Diseases of the respiratory system (J00-J99)	3	1.83	1	2.70	4	1.99
13: Diseases of the musculoskeletal system and connective tissue (M00-M99)	3	1.83	1	2.70	4	1.99
12: Diseases of the skin and subcutaneous tissue (L00-L99)	4	2.44	.	.	4	1.99
05: Mental and behavioral disorders (F01-F99)	.	.	3	8.11	3	1.49
02: Neoplasms (C00-D49)	1	0.61	1	2.70	2	1.00
17: Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	2	1.22	.	.	2	1.00
07: Diseases of the eye and adnexa (H00-H59)	1	0.61	.	.	1	0.50
19: Injury, poisoning and certain other consequences of external causes (S00-T88)	.	.	1	2.70	1	0.50
All	164	100.00	37	100.00	201	100.00

(🖫 Tab. 03-01-03)

Table 100: Prior/concomitant diseases by treatment

	Treatment					
	IM<ImmuneMonitoring>		UC<UnguidedControl>		All	
	N	PctN	N	PctN	N	PctN
ICD-10 Chapter						
04: Endocrine, nutritional and metabolic diseases (E00-E89)	42	35.59	26	31.33	68	33.83
09: Diseases of the circulatory system (I00-I99)	25	21.19	17	20.48	42	20.90
03: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	13	11.02	8	9.64	21	10.45
11: Diseases of the digestive system (K00-K94)	4	3.39	7	8.43	11	5.47
23: Surgical and other procedures (Ext.)	3	2.54	6	7.23	9	4.48
01: Certain infectious and parasitic diseases (A00-B99)	5	4.24	2	2.41	7	3.48
18: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	6	5.08	.	.	6	2.99

	Treatment					
	IM<ImmuneMonitoring>		UC<UnguidedControl>		All	
	N	PctN	N	PctN	N	PctN
06: Diseases of the nervous system (G00-G99)	3	2.54	3	3.61	6	2.99
21: Factors influencing health status and contact with health services (Z00-Z99)	3	2.54	2	2.41	5	2.49
14: Diseases of the genitourinary system (N00-N99)	3	2.54	2	2.41	5	2.49
10: Diseases of the respiratory system (J00-J99)	2	1.69	2	2.41	4	1.99
13: Diseases of the musculoskeletal system and connective tissue (M00-M99)	2	1.69	2	2.41	4	1.99
12: Diseases of the skin and subcutaneous tissue (L00-L99)	4	3.39	.	.	4	1.99
05: Mental and behavioral disorders (F01-F99)	2	1.69	1	1.20	3	1.49
02: Neoplasms (C00-D49)	.	.	2	2.41	2	1.00
17: Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	.	.	2	2.41	2	1.00
07: Diseases of the eye and adnexa (H00-H59)	.	.	1	1.20	1	0.50
19: Injury, poisoning and certain other consequences of external causes (S00-T88)	1	0.85	.	.	1	0.50
All	118	100.00	83	100.00	201	100.00

(🖫 Tab. 03-01-04)

Table 101: Mean number of prior/concomitant diseases

Treatment	N	Mean	Std Dev	Std Err	Minimum	Maximum
IM<ImmuneMonitoring>	21	5.6190	2.3553	0.5140	1.0000	11.0000
UC<UnguidedControl>	14	5.9286	3.1000	0.8285	1.0000	11.0000
Diff (1-2)		-0.3095	2.6736	0.9225		

P=0.7393 (TTest, equal variances)
(🖫 Tab. 03-01-01)

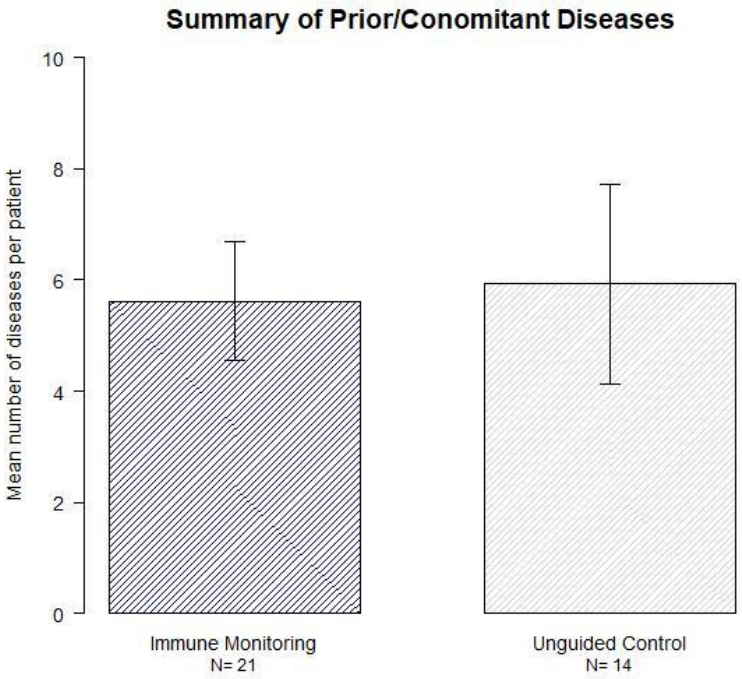

Figure 17: Summary of Prior/concomitant diseases

(🖫 Tab. 03-01-02)

Table 102: Incidence of prior diseases by treatment

ICD-10 chapter	Treatment N	(%)	Control N	(%)	Total N	(%)	P
01: Certain infectious and parasitic diseases (A00-B99)	4	19.05	2	14.29	6	17.14	1.0000
02: Neoplasms (C00-D49)	0	0.00	1	7.14	1	2.86	0.4000
03: Diseases of the blood and blood-forming organs and certa	1	4.76	2	14.29	3	8.57	0.5508
04: Endocrine, nutritional and metabolic diseases (E00-E89)	2	9.52	2	14.29	4	11.43	1.0000
05: Mental and behavioral disorders (F01-F99)	2	9.52	1	7.14	3	8.57	1.0000
06: Diseases of the nervous system (G00-G99)	0	0.00	2	14.29	2	5.71	0.1529
09: Diseases of the circulatory system (I00-I99)	1	4.76	1	7.14	2	5.71	1.0000
10: Diseases of the respiratory system (J00-J99)	1	4.76	0	0.00	1	2.86	1.0000
11: Diseases of the digestive system (K00-K94)	2	9.52	2	14.29	4	11.43	1.0000
13: Diseases of the musculoskeletal system and connective ti	1	4.76	0	0.00	1	2.86	1.0000
14: Diseases of the genitourinary system (N00-N99)	0	0.00	1	7.14	1	2.86	0.4000
18: Symptoms, signs and abnormal clinical and laboratory fin	1	4.76	0	0.00	1	2.86	1.0000
19: Injury, poisoning and certain other consequences of exte	1	4.76	0	0.00	1	2.86	1.0000
21: Factors influencing health status and contact with healt	0	0.00	1	7.14	1	2.86	0.4000
23: Surgical and other procedures (Ext.)	2	9.52	2	14.29	4	11.43	1.0000

ICD-10 chapter	Treatment N	(%)	Control N	(%)	Total N	(%)	P
Total	21	100.00	14	100.00	35	100.00	.

(🖫 Tab. 03-01-07b)

Table 103: Incidence of concomitant diseases by treatment

ICD-10 chapter	Treatment N	(%)	Control N	(%)	Total N	(%)	P
02: Neoplasms (C00-D49)	0	0.00	1	7.14	1	2.86	0.4000
03: Diseases of the blood and blood-forming organs and certa	12	57.14	5	35.71	17	48.57	0.3053
04: Endocrine, nutritional and metabolic diseases (E00-E89)	16	76.19	9	64.29	25	71.43	0.4736
06: Diseases of the nervous system (G00-G99)	3	14.29	1	7.14	4	11.43	0.6350
07: Diseases of the eye and adnexa (H00-H59)	0	0.00	1	7.14	1	2.86	0.4000
09: Diseases of the circulatory system (I00-I99)	21	100.00	14	100.00	35	100.00	.
10: Diseases of the respiratory system (J00-J99)	1	4.76	2	14.29	3	8.57	0.5508
11: Diseases of the digestive system (K00-K94)	2	9.52	4	28.57	6	17.14	0.1907
12: Diseases of the skin and subcutaneous tissue (L00-L99)	3	14.29	0	0.00	3	8.57	0.2588
13: Diseases of the musculoskeletal system and connective ti	1	4.76	2	14.29	3	8.57	0.5508
14: Diseases of the genitourinary system (N00-N99)	3	14.29	1	7.14	4	11.43	0.6350
17: Congenital malformations, deformations and chromosomal a	0	0.00	2	14.29	2	5.71	0.1529
18: Symptoms, signs and abnormal clinical and laboratory fin	4	19.05	0	0.00	4	11.43	0.1334
21: Factors influencing health status and contact with healt	3	14.29	1	7.14	4	11.43	0.6350
23: Surgical and other procedures (Ext.)	1	4.76	3	21.43	4	11.43	0.2794
Total	21	100.00	14	100.00	35	100.00	.

(🖫 Tab. 03-01-07a)

13.5 Summary of Safety Results and Conclusions

The overall safety findings showed a total of 211 adverse events (AE) (146 in the immune guided group and 65 in the unguided control). The majority of the events were mild to moderate with no differences between treatment groups. Only 49 AE (23.2%) were considered to have a causal relationship to study medication.

All patients had at least one AE. The most common AE System Organ Classes (SOCs) were Investigations (76%) > Infections and infestations (57%) > Gastrointestinal disorders (52%) > Blood and lymphatic system disorders (38%) > Immune system disorders (38%) in the IM group and Investigations (57%) > Infections and infestations (50%) > Nervous system disorders (50%) > Immune system disorders (36%) > Injury, poisoning and procedural complications (36%) in the UC group. On the preferred term level the highest incidence were kidney transplant rejection (34%), tremor (31%) and diarrhea (26%) with no differences between treatment groups. 27 patients (77%) had at least one treatment related AE with the highest incidence in the SOCs infections and infestations (37%), nervous system disorders (29%), and investigations (23%).

In each group one patient was withdrawn from the study product due to an adverse event.

A total of 21 SAE was reported (12 in the IM and 9 in the UC group), only 7 were rated as treatment related. The incidence of patients reporting a serious adverse event was 33% in the IM and 43% in the UC group.

The overall safety profile of the study medications was as expected from previous experience in renal transplant patients. No differences were detected between the treatment groups.

No safety concerns were identified in the laboratory data or vital signs reported during the study.

14 DISCUSSION AND OVERALL CONCLUSIONS

14.1 Discussion

The study conduct was not without problems. First the recruitment was much slower than anticipated and finally the recruitment was impossible for a while due to the corona pandemic, which finally led to the premature discontinuation of the trial.

Second the study was accompanied by some administrative problems as a result of a very demanding study design. Especially the immune monitoring procedures required complex interactions between the laboratory, the investigator and others involved in the management of the patients after discharge from the hospital.

At the end of the study only 3 patients (all in the IM group) were INFγ and DSA negative and had no BPAR, all others switched back to the scheme of the unguided control at some time point during the study demonstrating that only a small portion of the patients would enjoy a prolonged dose reduction.

After the study has been prematurely terminated the sample size is too small to prove the postulated better renal function in the immune monitored group. Therefore, the results should be interpreted in an exploratory manner. The use of p-values (and the use of the term “statistically significant” for a $p<0.05$) for secondary and other endpoints should be used only for descriptive purposes and cannot be used to support a confirmatory statement.

14.2 Conclusions

After premature discontinuation of the study, the data analysis does not show any relevant differences between the treatment arms. The primary analysis 12 months after transplantation could not prove a difference in renal function measured as eGFR by the 4 variable MDRD formula between a immune guided minimization compared to the unguided control. The results of the primary endpoint are consistent with secondary endpoints and a per protocol analysis.

The study hypothesis of a better renal function measured as eGFR according to the 4-varlable formular could not be proven with the final sample size.

Adverse events and serious adverse events were as expected for the study population. Safety analyses sowed no notable differences between the treatment groups. The safety data are consistent with the known safety profile of immunosuppression with tacrolimus, mycophenolic acid and prednisolone.

The study did not find any evidence of a safety risk for the study treatment compared to the control.

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

15.1 Patient Identification

Table 104: Patient identification List

Patient	Site-Id	Pat-ID	Date of transplantation(e)	Contract	ITT	PP	SAF	Treatment Arm
1	1-Großhadern	1	24/05/16	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
2	1-Großhadern	2	01/06/16	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
3	1-Großhadern	3	17/06/16	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
4	1-Großhadern	4	15/09/16	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
5	1-Großhadern	5	30/11/16	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
6	1-Großhadern	6	18/01/17	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
7	1-Großhadern	7	25/01/17	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
8	1-Großhadern	8	15/02/17	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
9	1-Großhadern	9	22/02/17	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
10	1-Großhadern	10	10/05/17	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
11	1-Großhadern	11	12/07/17	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
12	1-Großhadern	12	08/11/17	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
13	1-Großhadern	13	15/11/17	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
14	1-Großhadern	14	22/11/17	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
15	1-Großhadern	15	06/12/17	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
16	1-Großhadern	16	10/01/18	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
17	1-Großhadern	17	07/02/18	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
18	1-Großhadern	18	11/04/18	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
19	1-Großhadern	19	25/04/18	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
20	1-Großhadern	20	09/05/18	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
21	1-Großhadern	21	23/05/18	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
22	1-Großhadern	22	11/07/18	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
23	1-Großhadern	23	04/07/18	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
24	1-Großhadern	24	22/08/18	ASTELLAS	Yes	No	Yes	IM<ImmuneMonitoring>
25	1-Großhadern	25	14/11/18	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
26	1-Großhadern	26	23/01/19	ASTELLAS	Yes	Yes	Yes	IM<ImmuneMonitoring>
27	1-Großhadern	27	13/02/19	ASTELLAS	Yes	Yes	Yes	UC<UnguidedControl>
28	1-Großhadern	28	28/02/19	ASTELLAS	Yes	No	Yes	UC<UnguidedControl>
29	1-Großhadern	29	21/03/19	CHIESI	Yes	No	Yes	IM<ImmuneMonitoring>

Patient	Site-Id	Pat-ID	Date of transplantation(e)	Contract	ITT	PP	SAF	Treatment Arm
30	1-Großhadern	30	04/04/19	CHIESI	Yes	No	Yes	IM<ImmuneMonitoring>
31	1-Großhadern	31	12/06/19	CHIESI	Yes	No	Yes	IM<ImmuneMonitoring>
32	1-Großhadern	32	10/07/19	CHIESI	Yes	Yes	Yes	UC<UnguidedControl>
33	1-Großhadern	33	24/07/19	CHIESI	Yes	Yes	Yes	UC<UnguidedControl>
34	1-Großhadern	34	13/08/19	CHIESI	Yes	Yes	Yes	IM<ImmuneMonitoring>
35	1-Großhadern	35	15/01/20	CHIESI	Yes	No	Yes	IM<ImmuneMonitoring>

(🖫 Tab. 01-01-36)

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17 AUTHORSHIP AND APPROVAL

Study Title:	Anti-donor alloreactivity-guided CNI minimization versus unguided standard triple therapy in living-donor kidney transplantation
Protocol ID	ICANMINI
EudraCT-No.:	2015-002465-28

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

Sponsor Delegated Person (Coordinating principal investigator):

Prod. Dr. med. Markus Guba
Printed Name

Date, Signature

Author and project manager
at Algora Gesellschaft für Medizinstatistik und Vertriebssysteme mbH:

Dr. Karl Fehnle
Printed Name

Date, Signature

18 APPENDICES

18.1 Study Information

18.1.1 Protocol and Protocol Amendments

The study was started with the 2nd final protocol, dated 28.01.2016 which was amended once. Both, the final version and the Amendment 01, dated 30.01.2019 will be attached.

18.1.2 Sample CRF

An eCRF has been used and no printed version has been produced. An annotated CRF has been printed to a PDF file right out of the eCRF.

18.1.3 Statistical Analysis Plan

The statistical analysis plan dated 07-Feb-200 and signed 18-Feb-2022 is the final version for the analysis of the study.

18.1.4 List of IEC's or IRB's and representative written information for patient and sample consent forms

The study had a positive opinion of the following Ethics Committee

Ethikkommission der Med. Fakultät
der LMU München
Prof. Dr. Wolfgang Eisenmenger
Pettenkoferstr. 8a
80336 München

Due to the mono centric nature of the study no other ECs were involved.

18.1.5 Sample Informed Consent Form

The following informed consent forms have been used:

ICF Recipient Version 2.0, dated 28.01.2016
ICF Recipient Version 2.1, dated 28.08.2018

ICF Recipient Version 3.0, dated 30.01.2019

ICF Donor Version 2.0, dated 28.01.2016
ICF Donor Version 2.1, dated 28.08.2018
ICF Donor Version 3.0, dated 30.01.2019

Version 2.0 was implemented with the regulatory approval of the study version 2.1 was necessary to implement the requirements of the General Data Protection Regulation (GDPR) and version 3.0 implements changes made in amendment 01 to the protocol.

18.2 Tables and Listings

Complete program output containing tables and listings will be provided electronically in PDF-format. References to the appendix are marked with the 🖫 symbol throughout the text of this report.