Clinical Study Summary

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.

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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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 were 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) was 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 received 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 PR-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 unguided 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, 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 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.

Amendment: Envarsus® was introduced as equivalent to Advagraf® with amendment 01.

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 (biopsy proven acute rejection)
- 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

The study was stopped early due to the difficult recruitment situation, especially after the onset of the COVID-19 pandemic.

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 complete 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, defined as eGFR calculated according to the 4 variable MDRD formula at 12 months after transplantation showed a numerically lower eGFR in the immune monitored group with no statistically significant difference. At study discontinuation, 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 the CKD-EPI formula did 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 did not show significant differences between immune guided CNI minimization and unguided control in the primary analysis (eGFR by the MDRD-4 formula 12 months after transplantation) as well as in secondary endpoints and a per protocol analysis, but data interpretation is limited after early termination of the study. No evidence was found that the proposed alloimmune guided tacrolimus minimization would 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