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SYNOPSIS

Title of Study: Investigating New Onset Diabetes Mellitus in Kidney Transplant Recipients Receiving an Advagraf-Based Immunosuppressive Regimen With or Without Corticosteroids – A Multicenter, Two Arm, Randomized, Open Label Clinical Study

Investigator/Coordinating Investigator:

The principal investigator was [redacted] France.

Study Centers:

This was a multi-center study performed in 99 centers in 24 countries (Australia, Belgium, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Republic of Korea, Latvia, Lithuania, Mexico, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovak Republic, Spain, Sweden, and Switzerland).

Publication (reference):

Not applicable.

Study Period:

Date of first enrollment (Study initiation date): 22 January 2011

Date of last evaluation (Study completion date): 22 May 2013

Phase of Development: Phase 4

Objectives:

The primary objective of this study was to compare Arm 1 with Arm 2 with regard to incidence of new onset diabetes after transplantation (NODAT) as per American Diabetic Association (ADA) criteria [2010] at any point up to 24 weeks after kidney transplantation.

The secondary objective was to compare the safety and efficacy profiles of the 2 therapy regimens with each other.

Methodology:

This was a prospectively randomized, multi-center, multi-national Phase 4 open-label parallel-group study.

Patients about to undergo kidney allograft transplantation who satisfied all selection criteria were randomized to receive Advagraf + Basiliximab + Mycophenolate mofetil (MMF) + Steroids (discontinued at 10 days; Arm 1) or Advagraf + Basiliximab + MMF + Steroids (optional intra-operative bolus only; Arm 2) for 24 weeks.

Assessments were performed at baseline (visit 1; within 96 hours prior to surgery), day 1 (visit 2; the day after transplantation), and then at week 1, 2, 4, 8 and 12 (visits 3 to 7) and at the end of the study (visit 8; week 24).

Once a patient had completed or was discontinued from the study (prematurely or after 24 weeks), further immunosuppressive treatment was left to the discretion of the investigator.

A Data Safety Monitoring Board (DSMB) was convened to continuously monitor the safety profile of the study patients and the continuation of the study according to the protocol.

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Name of Active Ingredient: Tacrolimus		

Number of Patients (planned, enrolled and analyzed):

About 1166 patients were planned to be randomized and transplanted in this study; 583 per treatment arm. A total of 1167 patients were screened, of which 1166 were randomized in eCRF and 1125 patients were transplanted. Of the 1166 randomized patients, 28 patients did not receive ≥ 1 dose of study medication. The SAF thus consisted of 1138 patients; 561 patients were randomized in Arm 1 and 577 to Arm 2. The ITT consisted of 1122 patients who were randomized and transplanted. The FAS consisted of 1081 patients who were enrolled in the study, were transplanted, received at least 1 dose of any study medication and had ≥ 1 post-baseline estimation of the primary variable. The PPS consisted of 837 patients, i.e., all patients from the FAS who did not have any major protocol deviations.

Diagnosis and Main Criteria for Inclusion:

Eligible patients were men and women, ≥ 18 years, who had end stage kidney disease and were a suitable candidate for primary renal transplantation or re-transplantation (unless the graft was lost from rejection within 1 year). Eligible patients should have received a kidney transplant from a deceased or living (non-human leukocyte antigen [HLA] identical) donor with compatible ABO blood type. Female patients of childbearing potential had to be negative for pregnancy tests.

Test Product, Dose and Mode of Administration, Batch Numbers:

Advagraf capsules were dosed pre-operative at 0.1 mg/kg orally in 1 dose, and post-operative the initial dose was 0.2 mg/kg per day orally in 1 dose, where after subsequent Advagraf doses were adjusted on the basis of clinical efficacy and adverse events (AEs) following the tacrolimus whole blood trough concentrations in the blood.
Batch numbers: Advagraf 0.5 mg: [redacted]; Advagraf 1.0 mg: [redacted] Advagraf 3.0 mg: [redacted]; Advagraf 5.0 mg: [redacted].

Basiliximab was administered intravenous in 2 doses: 20 mg within 2 hours before transplantation at day 0 and 20 mg at day 4.
Batch numbers: [redacted].

MMF was dosed pre-operative at 1 g orally and post-operative at 1 g twice daily for the first 14 days (1.5 mg bid for Black or African-American patients). Thereafter the daily dose was reduced to 0.5 g twice daily.
Batch numbers: [redacted].

Corticosteroids were considered concomitant immunosuppressive treatment in the present study. All patients (in Arm 1 and Arm 2) received at day 0 a single intra-operative intravenous bolus in both arms at a dose between 0 mg to 1000 mg, dependent on center's policy. All patients at a center received the same standard dose.
In Arm 1, patients received oral prednisolone or equivalent for 10 days; 20 mg/d on day 1 to 4, 15 mg/d on day 5 and 6, 10 mg/d on day 7 and 8 and 5 mg/d on day 9 and 10. In Arm 2, corticosteroid administration was optional (i.e. only administered for treatment of acute rejection). Corticosteroids were not provided by the Sponsor (except for study participants in Sweden).

Duration of Treatment (or Duration of Study, if applicable):

The study duration was 24 weeks.

Name of Sponsor/Company: Astellas Pharma Europe Ltd		
Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable.

Criteria for Evaluation:

The primary efficacy endpoint was the diagnosis of NODAT as per ADA criteria [2010] at any point up to 24 weeks after kidney transplantation, defined as 1) glycated hemoglobin ($HbA1_c$) ≥ 6.5% at or after the week 12 visit, or 2) fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), or 3) 2-hr plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT), or 4) Symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L). HbA1c was measured at baseline, and at weeks 12 and 24. OGTT was performed at week 8 and week 24. Glucose was measured at all study visits.

Secondary efficacy variables were:

- Efficacy failure, defined using a composite endpoint consisting of any of the following:
  - graft loss (defined as re-transplantation, nephrectomy, death or dialysis ongoing at study end or at time of discontinuation of the patient from the study unless superseded by follow-up information)
  - Biopsy-confirmed Acute Rejection (BCAR)
  - Renal or graft dysfunction, defined as glomerular filtration rate (GFR) < 30 mL/min per 1.73m^2 estimated by modification diet in renal disease (MDRD) 4 formula at 24 weeks after transplantation
- Efficacy failure or NODAT, as the composite of the primary variable and efficacy failure.
- Incidence of 2-h plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) during the OGTT at week 8 and/or 24 (must be at least 4 weeks after treatment with steroids e.g. for treatment of rejection).
- Change from baseline (visit 1) in HbA_{1c} levels at weeks 12 and 24.
- The first ADA criterion met. If multiple ADA criteria were met simultaneously, patients were counted under each criterion met.
- Acute rejections (as determined by the investigator and reported in the eCRF):
  - Number of patients and time to first acute rejection
  - Number of patients and time to first corticosteroid-resistant acute rejection (as determined by medical review)
  - Overall frequency of acute rejection episodes
- Category of acute rejection. All rejection episodes (regardless of whether diagnosed by signs and symptoms only or assessed as BCAR) were classified by medical review in to:
  - Spontaneously Resolving Acute Rejection
  - Corticosteroid Sensitive Acute Rejection
  - Corticosteroid Resistant Acute Rejection
  - Antibody Responsive Acute Rejection
  - Antibody Resistant Acute Rejection
- BCAR
  - Number of patients and time to first incidence of BCAR
  - Number of patients and time to first incidence of biopsy-confirmed corticosteroid-resistant acute rejection
  - Overall frequency of BCAR episodes
  - T-cell mediated BCAR
  - Antibody mediated BCAR
  - Severity of BCAR episodes
- Graft survival.

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

- Delayed graft function (defined as the patient having dialysis for > 1 day during the first week post transplantation [day 1 to day 7]).
- Renal function at week 24 after transplantation, assessed by calculated GFR with MDRD4 formula, and by calculated creatinine clearance with Cockcroft Gault formula, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
- Patient survival.

Other efficacy variables included:

- Patient reported outcomes determined using the EuroQoL 5-Dimensions (EQ-5D) questionnaire
- Use of resources
- Biomarkers to measure renal injury in urine and donor specific antibody reactivity in blood

Safety was assessed from the incidence and severity of (serious) adverse events ([S]AEs), change from baseline in clinical laboratory evaluations (biochemistry, hematology and urinalysis) and vital signs. Blood samples for measurement of tacrolimus concentrations in whole blood were also taken.

Statistical Methods:

Efficacy

The primary variably was primarily analyzed using the Kaplan-Meier estimate for the NODAT rate at week 24 and the corresponding 2-sided 95%-confidence intervals (CIs) were constructed and compared between the treatment arms. If the CI did not contain 0 then the equality of NODAT rates in each arm was rejected. The first ADA criterion met was summarized for all patients by treatment arm and criterion. In addition, the primary variable was analyzed descriptively by center and treatment arm. These primary analyses were performed using the FAS.

As secondary analysis the primary analysis was repeated for the PPS and by demographic subgroup (gender, race and age [< 50 years and ≥ 50 years] for the FAS and PPS. The difference in Arm 1 and Arm 2 for NODAT rate at week 24 was assessed with a continuity-corrected chi-square test for the ITT set. The primary variable was also analyzed using conditional logistic regression, stratified by site, gender, race and age (< 50 years and ≥ 50 years).

The secondary efficacy variables (time to efficacy failure, time to efficacy failure or NODAT, rate of acute rejections by signs and symptoms, rate of corticosteroid-resistant acuter rejection, rate of BCAR and rate of corticosteroid resistant BCAR, rate of graft and patient survival), were analyzed similarly as the primary analysis using Kaplan-Meier estimates and corresponding 95%-CIs for comparison between treatment arms. In addition, the incidence of these secondary variables, and number and percentage of patients with delayed graft function, and rate of OGTT ≥ 200 mg/dL were analyzed with the chi-square test. The classification of acute rejections episodes was also summarized by treatment arms. Analysis of variance (ANOVA) was used to test the differences between the treatment arms for renal function assessed by GFR calculated by MDRD4 formula, creatinine clearance calculated by Cockcroft-Gault formula and by CKD-EPI at week 24, and change from baseline in HbA1c levels at week 12 and week 24. Analysis of the secondary efficacy variables were performed for both the ITT and PPS.

The incidence of renal dysfunction (MDRD4) at week 24 was analyzed using a Cox proportional hazards model adjusting for treatment and donor age (< 30, 31-40, 41-50, 51-60, 61-70, > 70 years).

The patient-reported outcome questionnaire (EQ-5D) was analyzed descriptively. Additionally, the change from baseline (before or within 10 days after transplantation) to week 24 (or last available observation after week 4) for the visual analogue scale (VAS) and EQ-5D index were analyzed by means of an analysis of

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

covariance (ANCOVA) model, with treatment arm and center as fixed factors and age and baseline value as covariates.

Resource use was summarized descriptively by treatment arm. Biomarkers of kidney injury and donor specific antibody reactivity, and change from baseline for these variables, were summarized, using descriptive statistics, by treatment arm and efficacy failure, using the ITT analysis set.

Safety

All AEs were summarized. The number and percentage of patients with treatment-emergent (TE)AEs, classified by system organ class (SOC) and preferred term (PT) were summarized for each treatment group and overall. Similar summaries were provided for drug-related TEAEs, serious TEAEs, serious drug-related TEAEs, serious drug-related TEAEs that led to study drug discontinuation, TEAEs that led to study drug discontinuation, drug-related TEAEs that led to study drug discontinuation, TEAEs of special interest, common TEAEs (i.e., TEAEs that occurred in ≥ 5% and ≥ 10% of the patients in any treatment arm), TEAEs leading to death and drug-related TEAEs leading to death. TEAEs and drug-related TEAEs were also summarized by severity and by relationship (all TEAEs only) to the study drug. Selected AE summaries were additionally provided by sex, age group (< 50, ≥ 50 years) and donor status (cadaveric, non-cadaveric).

Hematology, biochemistry and urinalysis test results and vital signs, including changes from baseline, were summarized descriptively at each visit by treatment arm.

Summary of Results/Conclusions:

Population:

A total of 1167 patients were screened, and all except 1, were randomized in eCRF. Of the randomized patients, 1138 took ≥ 1 dose of study medication (SAF) and 1081 patients were transplanted, took ≥ 1 dose of study medication and had ≥ 1 post-baseline estimation of the primary variable (FAS) (Figure 1).

Two hundred and two patients withdrew early, with as main reasons AEs (103 patients [9.1%]), protocol violation (23 patients [2.0%]) and withdrawal of consent (13 patients [1.1%]).

Demographics and baseline characteristics for the SAF were well-matched between the treatment arms (Table 1). Similar results were found for FAS and PPS.

Complications during the kidney transplantation were recorded in the SAF for 4.2% of patients in Arm 1 and for 3.0% of patients in Arm 2. Otherwise, there were no relevant differences between treatment arms.

The most common primary diagnosis for kidney transplant in the SAF was polycystic kidney disease in 22.6% of patients in Arm 1 and 24.0% of patients in Arm 2. Other common reasons (reported for ≥ 10% of patients) were glomerulonephritis (13.9% and 18.9% of patients, respectively) and hypertensive nephrosclerosis (15.5% and 11.1%). The diagnosis was unknown in 10.6% of patients overall. Overall, 2.9% of patients had undergone a previous kidney transplant (2.3% of patients in Arm 1 and 3.4% of patients in Arm 2); the median time since the previous transplant was 13 years [Table 2].

Patients in the SAF received an overall mean initial dose of Advagraf of 0.16 mg/kg, and the mean Advagraf dose on day 0 and day 1 was 0.14 and 0.19 mg/kg, respectively. Advagraf dose adjustments were made for 98.3% of the patients overall. Tacrolimus whole blood trough levels were generally within the recommended ranges.

Over 96% of all SAF patients received both doses of basiliximab. Only 1 dose of basiliximab was received by approximately 3% of all patients (3.4% of patients in Arm 1 and 2.4% of patients in Arm 2). The first dose was

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

given between day -1 and day 3, and the second dose between day 2 and day 6. There were no relevant differences between treatment arms.

The overall mean dose of mycophenolate mofetil (MMF) in the SAF population was 1.4 g on day 0 (prior to transplantation), about 2.0 g on days 1 to 14, 1.1 g on day 28, and 1.0 g on days 56, 84 and 168. The overall mean dose of MMF at the end of the study was 1.1 g. Dose adjustments were made for 96.7% patients overall.

The median duration of treatment with corticosteroids in the SAF was 11 days in Arm 1 and 1 day in Arm 2, and the median of the total steroid (cumulative) dose received in Arm 1 is 765 mg compared to 625 mg in Arm 2, reflecting the treatment regimen per protocol. The mean cumulative dose of corticosteroids was higher in patients with NODAT compared to those without (2021 vs 1293 mg), with no clinically relevant difference between treatment arms. The mean number of treatment days was also higher (38.7 vs 19.9 days in Arm 1 and 28.9 vs 12.8 in Arm 2) in patients with NODAT compared to those without.

Efficacy Results:

Primary Efficacy Variable

Primary analysis

The primary analysis assessing equality of NODAT in Arm 1 to Arm 2 was performed on the FAS, using the Kaplan-Meier analysis. The Kaplan-Meier estimate of NODAT rate at week 24 was 17.4% in Arm 1 (77 patients) compared to 16.6% in Arm 2 (74 patients)(Table 3). The difference in the Kaplan-Meier estimate between the 2 arms (Arm 1 – Arm 2) was 0.8% and the corresponding 95% CI was -6.0% to 4.0%. As the 95% CI of the difference contained 0%, the equality of the NODAT rates between the treatment arms could not be rejected.

The most frequent first ADA criterion met was 'FPG ≥ 126 mg/dL' (40.4% of patients with NODAT), with a higher incidence in Arm 1 (44.2%) vs Arm 2 (36.5%). The second most frequent criterion was '2-h plasma glucose ≥ 200 mg/dL during an OGTT' (33.1% of patients with NODAT), with a slightly lower incidence in Arm 1 (29.9%) vs Arm 2 (36.5%). For the remaining criteria no clinically relevant differences between treatment arms were observed.

The number of patients in the subgroups was too small to draw any conclusions on analysis of total NODAT rate and first ADA criterion met, per country and center.

Secondary analyses

Similar results as for the primary analysis for the FAS were observed for the PPS. The most frequent first ADA criterion met for the PPS was '2-h plasma glucose ≥ 200 mg/dL during an OGTT' (42.3% of patients with NODAT), followed by FPG ≥ 126 mg/dL (7.0 mmol/L)' (37.8% of patients with NODAT), both with comparable incidences between the treatment arms. The overall incidence of 'HbA1c ≥ 6.5%' and 'symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL' was 15.3% and 4.5% of patients with NODAT, respectively, with a higher incidence in Arm 1 vs Arm 2 (17.3% and 13.6%) for 'HbA1c ≥ 6.5%' and with a higher incidence in Arm 2 vs Arm 1 (6.8% and 1.9%) for 'symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL'.

Results of the chi-square test for the ITT revealed no statistically significant differences in NODAT rate between the treatment arms (P = 0.4086).

Repeating the primary analysis by gender, race and age (< 50 years and ≥ 50 years) for the FAS and PPS demonstrated no significant differences in incidence of NODAT between the treatment arms (all P > 0.05).

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

Logistic regression analysis demonstrated that the estimated odds-ratio of having NODAT was not significantly different between Arm 1 and Arm 2, male vs female patients, White vs Black or African Americans and White vs Asian and all other races (all P > 0.572).

Secondary Efficacy Variables

The results of the Kaplan-Meier analysis for the time-to-event secondary efficacy variables are provided for the ITT in Table 4. The rates of efficacy failure, efficacy failure or NODAT, graft loss and deaths were comparable between the 2 treatment arms. The rate of acute rejection was statistically significantly higher in Arm 2 (25.9%) vs Arm 1 (18.2%; P = 0.0012). Also, the rate of BCAR is significantly higher in Arm 2 compared to Arm 1 (13.6% vs 8.7%; P = 0.0061). Results for the PPS were comparable.

The results of the chi-square analysis of efficacy failure, graft survival and patient survival were also not statistically significant for the ITT (P >0.2770) and PPS (P > 0.1110). Statistically significant results were also observed with chi-square analysis for acute rejections and BCAR (P = 0.0017 and P = 0.0091), but not for corticosteroid-resistant acute rejections (P = 0.3941 and P = 0.7071) [Table 12.3.3.4.1.1]. Similar results were obtained for the PPS.

For the ITT, the mean (SD) 2-h plasma glucose at week 8 was 8.15 (2.74) mg/dL in Arm 1 and 8.16 (2.83) mg/dL in Arm 2. The levels at week 24 were 7.26 (2.46) mg/dL in Arm 1 and 7.33 (2.50) mg/dL in Arm 2. The rate of 2-h plasma glucose ≥ 200 mg/dL at week 24 was 5.1% in both treatment arms for the ITT. The number of patients with 2-h plasma glucose ≥ 200 mg/dL at week 8 or 24 (worst value) was 65 (11.8%) in Arm 1 and 62 (10.9%) in Arm 2, and this was not statistically significantly different between the treatment arms (P = 0.6878). The comparisons between treatment arms for the PPS were also not statistically significant.

The difference in Least Square-mean change from baseline in HbA1c levels between the 2 arms in the ITT was -0.04 at week 12 and 0.01 at week 24 and was not statistically significant for both time points (P = 0.445 and P = 0.861, respectively). Treatment comparisons for the PPS were also not statistically significant.

The classification of acute rejections and BCARs is provided for the ITT in Table 5. The acute rejections were most commonly classified as corticosteroid sensitive, for those by signs and symptoms (13.4%) as well as for the BCARs (6.4%), with lower rates in Arm 1 (10.2% and 4.2%, respectively) as compared to Arm 2 (16.5% and 8.6%). Similar results were observed for the PPS.

In the ITT, there were slightly more patients with delayed graft function in Arm 2 than in Arm 1 (29.1% vs 27.8%), but the difference between the rates was not statistically significant (P = 0.6283). Results for PPS were comparable.

The descriptive statistics for renal function assessments are provided in Table 6. After 24 weeks of treatment there were no significant differences between treatment arms in renal function (all P > 0.2). The incidence of renal or graft dysfunction in the ITT was 10.3% (57 patients) in Arm 1 and 9.6% (55 patients) in Arm 2, with no statistically significant difference between the 2 arms (P = 0.6906). Similar results were observed for the PPS. Analyses of renal dysfunction using a Cox proportional hazards model adjusting for treatment and donor age, showed no statistically significant difference between Arm 1 (10.3%) vs Arm 2 (9.6%). The risk of renal dysfunction was however significantly lower for patients who received a kidney from a donor aged < 50 years (all P < 0.05), and significantly higher for those who received a kidney from a donor aged > 70 years (P = 0.0225), as compared to the donors aged between 51-60 years. Similar results were observed for the PPS, with the exception of the age group > 70 years. This subgroup was however small and results should therefore be interpreted with caution.

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

Other Efficacy Variables:

EQ-5D: Improvements were shown in the ITT for the domains 'usual activities', 'pain/discomfort', and anxiety/depression', with no clinically relevant differences between treatment arms. There were no clinically relevant changes from baseline to week 24 for the domains 'mobility' and 'self-care'. It should however be noted that the baseline value for the latter 2 domains was already relatively high and that there was thus less room for improvement (Table 7).

The patients' best imaginable health state improved in the ITT by an average of 16 points (on a 100-point VAS scale) (from 69 at baseline to 85 at week 24) in Arm 1, and 14 points (from 70 to 84) in Arm 2. The change from baseline to week 24 was not statistically significantly different between treatment arms (P = 0.749).

The change from baseline to week 24 in the EQ-5D summary index was for the ITT 0.058 in Arm 1 and 0.036 in Arm 2, and was also not statistically significantly different between treatment arms (P = 0.671).

Comparable results were observed for the PPS.

Resource use: For the ITT, the mean number of days in hospital was 24.6 in both treatment arms. More patients in Arm 2 stayed in the intensive care unit (ICU), and the mean duration of their stay was slightly longer compared to patients in Arm 1 (6.4 vs 5.7 days).

Biomarkers: The biomarkers of kidney injury (monocyte chemoattractant protein 1 [MCP1], interferon gamma-induced protein 10 [IP10] and urine creatinine quantitative [UCREATQQ]) are summarized by treatment arm and efficacy failure for the ITT at day 168 (end of study) in Table 8.

At the end of the study, the mean creatinine corrected MCP1 ratio was overall higher in Arm 2 (55.8 ng/mmol) vs Arm 1 (49.1 ng/mmol). For both treatment arms, the levels were higher in the subgroup of patients with efficacy failure (75.0 ng/mmol in Arm 1 and 66.4 ng/mmol in Arm 2) as compared to the subgroup of patients with no efficacy failure (42.4 ng/mmol and 50.4 ng/mmol, respectively).

The overall mean creatinine corrected IP10 level at the end of the study was higher for Arm 2 (3.9 ng/mmol) vs Arm 1 (3.1 ng/mmol). For Arm 1, the level was higher in the subgroup of patients with efficacy failure (4.8 ng/mmol) as compared to the subgroup with no efficacy failure (2.7 ng/mmol), but was comparable between the subgroups in Arm 2 (4.0 ng/mmol vs 3.9 ng/mmol).

Overall, the mean UCREATQQ at the end of the study was comparable in both treatment arms (8.0 mmol/L in Arm 1 and 7.9 mmol/L in Arm 2). The mean UCREATQQ was lower in both treatment arms for the subgroup of patients with efficacy failure (6.9 and 7.6 mmol/L) as compared to the subgroups with no efficacy failure (8.3 and 8.0 mmol/L).

Very few subjects in the ITT had positive tests for donor specific antibodies present against HLA Class I or II. Hence there was little power to detect any association of antibodies with other factors. The association of antibodies with efficacy failure was weak. Overall, there were no clinically relevant changes in the incidence of patients with donor specific antibodies present against HLA Class I or II from baseline to the end of the study. There were 5 subjects detected with newly developed donor specific antibody in Arm 2 compared to 1 patient in Arm 1.

The mean cPRA, i.e., the proportion of the population to which the recipient would react via pre-existing antibodies, was slightly higher in Arm 1 vs Arm 2. At baseline, patients in the efficacy failure subgroup had higher mean cPRA than patients with no efficacy failure (10.7% vs 7.7% in Arm 1 and 8.6% vs 7.4% in Arm 2). No such difference was apparent at the end of the study.

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

Safety Results:

Over 90% of patients reported ≥ 1 AEs during the study, and around 60% of patients had ≥ 1 AEs that were considered related to treatment by the investigator (Table 9). AEs reported in ≥ 10% of patients in any treatment arm were anaemia (26.5% of patients overall), diarrhea (23.5%), hyperglycemia (21.2%), hyperkalemia (16.9%), complications of transplanted kidney (15.9%), kidney transplant rejection (15.6%), leukopenia (15.6%), nausea (13.6%), hypertension (13.6%), oedema peripheral (12.7%), urinary tract infection (12.0%), blood creatinine increased (11.5%) and constipation (11.2%). There were no notable differences between treatment arms, with the exception of kidney transplant rejection and hematuria, which were more frequent in Arm 2 (19.1% and 8.0%) than in Arm 1 (11.9% and 5.5%).

No single treatment-related AE PT was reported by ≥ 10% of patients in any treatment arm. The most commonly reported treatment-related AEs were hyperglycemia (reported by 9.4% of patients in Arm 1 and by 9.5% of patients in Arm 2), tremor (6.8% and 8.1%), diabetes mellitus (6.1% and 5.4%), urinary tract infection (5.5% and 5.2%) and kidney transplant rejection (3.2% and 6.2%).

Most AEs were of mild or moderate severity. Severe AEs that were reported by ≥ 2% of patients in any treatment arm were complications of transplanted kidney (reported by 3.0% of patients in Arm 1 and by 2.4% of patients in Arm 2), renal failure acute (2.0% and 2.1%) and kidney transplant rejection (2.9% and 3.8%). These were also the most commonly reported treatment-related AEs of severe intensity.

The summary of AEs by gender showed that of the most commonly reported AEs (i.e., AEs reported by ≥ 10% of patients in any treatment arm) diarrhea, nausea, urinary tract infection, anaemia and oedema peripheral were more frequent (i.e., a difference of ≥ 5% in any treatment arm) in female patients, and kidney transplant rejection and hyperkalemia tended to be more frequent in male patients. The summary of most common AEs by age showed that hyperglycemia, hyperkalemia, diarrhea, constipation, anaemia, leukopenia and oedema peripheral were more frequent in patients aged ≥ 50 years. Although in Arm 2, diarrhea was more often observed in patients < 50 years. The AE summary by organ donor type (cadaveric or non-cadaveric) was also provided, but as > 80% of donor organs were cadaveric, the numbers in the other subgroups were too small to make meaningful comparisons between subgroups.

Thirteen patients died, 8 (1.4%) in Arm 1 and 5 (0.9%) in Arm 2. Of the 13 deaths, 7 occurred during the treatment phase, and 6 occurred during follow-up. For 4 patients, the cause of death was considered related to treatment by the investigator; the events leading to death were 1 case of hepatitis acute and 1 case of pulmonary embolism in Arm 1, and 1 case of pneumonia and 1 case of pneumonia, sepsis and respiratory failure in Arm 2.

Overall, 46.1% of patients reported ≥ 1 SAEs, with comparable incidences between treatment arms, except for serious kidney transplant rejection which occurrence was higher in Arm 2 (11.3%) vs Arm 1 (7.7%). Overall, 6.1% of the patients discontinued treatment due to the occurrence of SAEs, with no difference between treatment arms. Treatment-related SAEs were reported by 18.7% of patients overall. Only kidney transplant rejection was reported by ≥ 2% of patients in any treatment arm, with no clinically relevant difference between treatments (2.3% of patients in Arm 1 and 4.2% in Arm 2).

The incidence of SAEs was slightly more common in female patients vs male patients (47.5% vs 45.4%), and also more common in patients aged ≥ 50 years compared to patients < 50 years (49.8% vs 42.0%). Also incidences for treatment-related SAEs were more common for females as compared to males (21.0% vs 17.6%), and in patients aged ≥ 50 years compared to patients < 50 years (21.7% vs 15.4%). The overall incidence of SAEs by organ donor type was between 44.0% and 47.4% of patients for all SAEs, and between 18.4% and 21.6% of patients for treatment-related SAEs. The incidence of SAEs for patients with an organ from a living donor was higher in Arm 1 than in Arm 2, but it should be noted that the number of patients in these 2

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Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

subgroups was low. There were no differences between treatment arms for patients with an organ from a cadaveric donor.

Overall, 7.9% of patients had ≥ 1 AEs that led to treatment discontinuation, most commonly kidney transplant rejection, reported by 2.0% of patients in Arm 1 and by 1.7% of patients in Arm 2. There were no other AEs that led to treatment discontinuation in ≥ 2% of patients in any treatment arm. Treatment-related AEs leading to permanent discontinuation were reported by 3.9% of patients overall.

The overall incidence of AEs leading to permanent discontinuation was 6.6% for female patients and 8.6% of male patients, and for only treatment- related AEs it was 2.6% for female patients and 4.5% for male patients, with no relevant differences between treatment arms. Of the patients < 50 years, 8.4% discontinued due to AEs, compared with 7.4% of patients aged ≥ 50 years. When only treatment-related AEs were considered, the percentages were 3.6% and 4.1%, respectively. There were no notable differences between treatment arms. Of the patients with an organ from a living non-related donor, 21.1% discontinued due to AEs, compared to 9.0% of patients with an organ from a living related donor, and 7.3% of patients with an organ from a cadaveric donor. When only treatment-related AEs leading to discontinuation were considered, these percentages were 7.9%, 5.2% and 3.6%, respectively. More patients with an organ from a living non-related donor in Arm 2 discontinued due to treatment-related AEs compared to Arm 1 (10.5% vs 5.3%), but it should be noted that the number of patients in this subgroup was low, and that results therefore must be interpreted with caution.

The overall incidences of AEs of special interest were comparable between the treatment arms (7.8% for diabetes mellitus AEs, 22.3% for neurological AEs, 14.5% for hypertension AEs and 26.5% for vascular AEs). AEs of diabetes mellitus and neurological AEs, were slightly more common in female patients compared to male patients, and also more common in patients aged ≥ 50 years than in patients < 50 years of age. Hypertension AEs and vascular AEs were more common in male patients as compared to female patients, and while hypertension AEs were more common in patients < 50 years of age as compared to patients aged ≥ 50 years, the opposite was observed for vascular AEs, i.e. a higher incidence in patients < 50 years vs older patients. For each of the AEs of special interest the number and percentages in the subgroups by donor status was too small to draw meaningful conclusions.

Most changes in biochemistry and hematology values were considered related to the transplantation, the surgical procedure or medications related to surgery. There were no clinically relevant differences between treatment arms. There were also no notable differences between treatment arms with urinalysis.

Overall, there were no treatment-associated clinically relevant changes from baseline to the end of the study in vital signs (blood pressure and pulse rate). There were also no notable differences between treatment arms.

CONCLUSIONS:

- The results from the Kaplan-Meier analysis showed no statistically significant difference in NODAT rates (the primary efficacy variable) between Arm 1 and Arm 2. The results for the FAS were confirmed by the results from the PPS, and by the results from the continuity-corrected chi-square test and the conditional logistic regression analysis adjusted for gender, race and age.
- There were also no statistically significant differences between Arm 1 and Arm 2 for the following secondary efficacy variables:
    - Rate of efficacy failure or the composite endpoint efficacy failure or NODAT
    - Change from baseline for the OGTT or HbA1c levels
    - Rate of graft survival or delayed graft function
    - Renal function, i.e., GFR by MDRD4 or calculated creatinine clearance
    - Patient survival

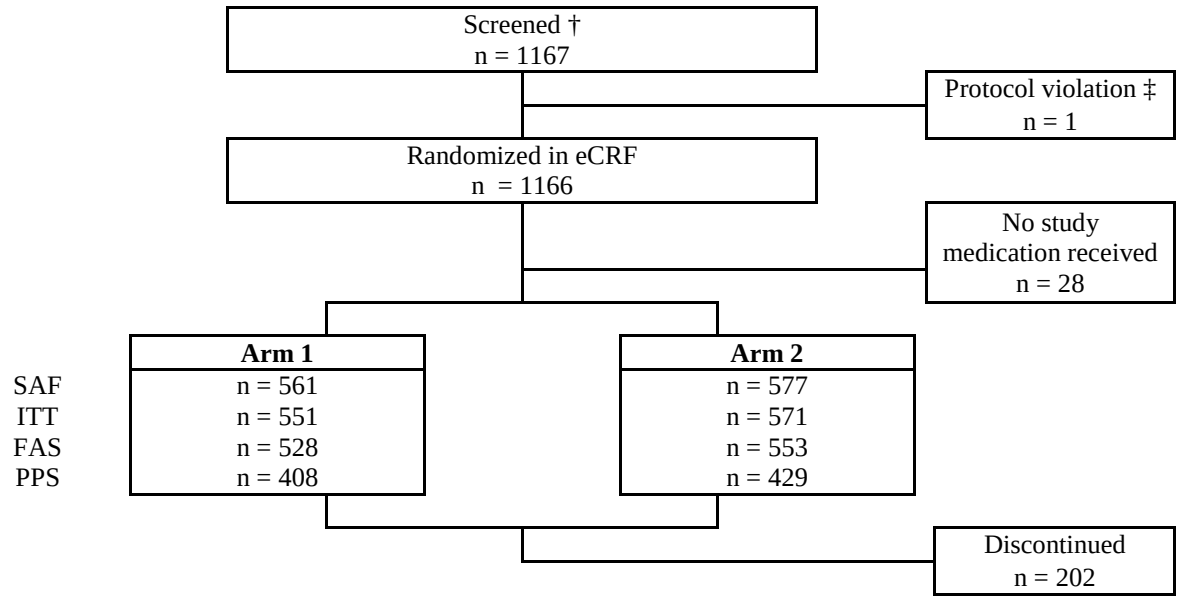
Name of Sponsor/Company: Astellas Pharma Europe Ltd		
Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

- The mean cumulative dose of corticosteroids was higher in patients with NODAT compared to those without (2021 vs 1293 mg), with no clinically relevant difference between treatment arms. In both treatment arms, the mean number of treatment days was also higher in patients with NODAT compared to those without.
- The rate of acute rejections and BCAR was statistically significantly higher in Arm 2 as compared to Arm 1, with a 7.7% and 4.9% difference between the arms, respectively (P = 0.0012 and P = 0.0061, respectively). There were no statistically significant differences between treatment arms in the rate of corticosteroid-resistant acute rejections.
- Patients in both treatment arms showed a clinically relevant improvement in their health state on the EQ-5D for the domains 'usual activities', 'pain/discomfort', and anxiety/depression', the EQ-5D summary index and the patient's best imaginable health state score. The EQ-5D summary index showed no statistically significant difference between the two arms.
- The number of days in hospital was comparable between treatment arms, but more patients in Arm 2 stayed in the ICU for a slightly longer period compared with patients in Arm 1, and more patients in Arm 2 compared to Arm 1 needed dialysis at the end of the study.
- The biomarker of kidney injury MCP1 was generally higher and UCREATQQ was generally lower in the subgroup of patients with efficacy failure compared to the subgroup of patients with no efficacy failure. No consistent pattern was observed for IP10.
- HLA antibodies detected in both arms of the study were largely present at baseline. The association between baseline antibodies and efficacy failure was weak.
- Mean panel reactive antibody (cPRA) was similar at baseline and at the end of the study in both arms. The association between efficacy failure and cPRA was weak.
- Both treatment arms had a similar safety profile, with the exception of kidney transplant rejection, which was more frequently reported in Arm 2 (19.1%) than in Arm 1 (11.9%).

In conclusion, of the 2 regimens studied, Arm 1 is the preferred immunosuppressive treatment in kidney transplant recipients as it does induce a comparable NODAT rate as in Arm 2, and it reduces the risk of biopsy-confirmed acute rejections, which occurred at a significant higher rate in Arm 2.

Date of Report: 19 December 2013

Figure 1 Patient Disposition



Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only)

FAS: full analysis set; ITT: intent to treat; PPS: per protocol set; SAF: safety analysis set

† This is the number of patients randomized in IVRS. All screened patients were randomized in IVRS, as the start of the study quickly followed screening.

‡ Patient [redacted] was randomized in IVRS but not in the eCRF.

Source: Tables 12.1.1.1 and 12.1.1.2, 12.1.1.3.1

Table 1 Demographic and Baseline Characteristics (SAF)

		Arm 1 (N = 561)	Arm 2 (N = 577)	Total (N = 1138)
Sex, n (%)	Male	376 (67.0)	381 (66.0)	757 (66.5)
	Female	185 (33.0)	196 (34.0)	381 (33.5)
Race, n (%)	White	474 (84.5)	495 (85.8)	969 (85.1)
	Black/African	13 (2.3)	5 (0.9)	18 (1.6)
	Asian	13 (2.3)	16 (2.8)	29 (2.5)
	Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)
	Other	60 (10.7)	60 (10.4)	120 (10.5)
Age (years)	Mean (SD)	49.55 (13.53)	49.95 (13.54)	49.75 (13.53)
	Median (Min, Max)	50.0 (18, 80)	51.0 (18, 80)	51.0 (18, 80)
	< 50, n (%)	264 (47.1)	269 (46.6)	533 (46.8)
	50 – 65, n (%)	228 (40.6)	242 (41.9)	470 (41.3)
	66 – 75, n (%)	61 (10.9)	61 (10.6)	122 (10.7)
	> 75, n (%)	8 (1.4)	5 (0.9)	13 (1.1)
Height (cm)	N	555	573	1128
	Mean (SD)	170.9 (9.6)	170.9 (9.6)	170.9 (9.6)
	Median (Min, Max)	172.0 (147, 205)	171.0 (134, 203)	172.0 (134, 205)
Weight (kg)	N	560	576	1136
	Mean (SD)	75.3 (15.1)	75.0 (15.1)	75.1 (15.1)
	Median	75.2	75.0	75.0
	(Min, Max)	(44.0,133.7)	(38.0,135.4)	(38.0,135.4)

Table continues on next page

		Arm 1 (N = 561)	Arm 2 (N = 577)	Total (N = 1138)
BMI (kg/m²)	N	555	573	1128
	Mean (SD)	25.7 (4.1)	25.6 (4.4)	25.6 (4.3)
	Median (Min, Max)	25.4 (16.5, 40.9)	25.0 (15.9, 44.7)	25.2 (15.9, 44.7)
HIV (Recipient), n (%)	Negative	555 (99.3)	573 (99.5)	1128 (99.4)
	Positive	0	0	0
HIV Mismatch (Recipient/ Donor), n (%)	Negative/Negative	551 (98.6)	568 (98.6)	1119 (98.6)
	Negative/Unknown	4 (0.7)	5 (0.9)	9 (0.8)
	Unknown/Negative	4 (0.7)	3 (0.5)	7 (0.6)
HBV (Recipient), n (%)	Negative	544 (97.3)	562 (97.6)	1106 (97.4)
	Positive	11 (2.0)	12 (2.1)	23 (2.0)
HBV Mismatch (Recipient/ Donor), n (%)	Negative/Negative	539 (96.4)	556 (96.5)	1095 (96.5)
	Negative/Unknown	5 (0.9)	6 (1.0)	11 (1.0)
	Positive/Negative	11 (2.0)	11 (1.9)	22 (1.9)
	Positive/Unknown	0	1 (0.2)	1 (0.1)
	Unknown/Negative	4 (0.7)	2 (0.3)	6 (0.5)
HCV (Recipient), n (%)	Negative	544 (97.3)	562 (97.6)	1106 (97.4)
	Positive	11 (2.0)	6 (1.0)	17 (1.5)
HCV Mismatch (Recipient/ Donor), n (%)	Negative/Negative	538 (96.2)	555 (96.4)	1093 (96.3)
	Negative/Unknown	6 (1.1)	7 (1.2)	13 (1.1)
	Positive/Negative	11 (2.0)	6 (1.0)	17 (1.5)
	Unknown/Negative	4 (0.7)	8 (1.4)	12 (1.1)
CMV (Recipient), n (%)	Negative	173 (30.9)	170 (29.5)	343 (30.2)
	Positive	351 (62.8)	382 (66.3)	733 (64.6)
CMV Mismatch (Recipient/ Donor), n (%)	Negative/Negative	72 (12.9)	70 (12.2)	142 (12.5)
	Negative/Positive	97 (17.4)	96 (16.7)	193 (17.0)
	Negative/Unknown	4 (0.7)	4 (0.7)	8 (0.7)
	Positive/Negative	84 (15.0)	102 (17.7)	186 (16.4)
	Positive/Positive	231 (41.3)	252 (43.8)	483 (42.6)
	Positive/Unknown	36 (6.4)	28 (4.9)	64 (5.6)
	Unknown/Negative	6 (1.1)	5 (0.9)	11 (1.0)
	Unknown/Positive	19 (3.4)	14 (2.4)	33 (2.9)
EBV (Recipient), n (%)	Negative	44 (7.9)	55 (9.5)	99 (8.7)
	Positive	430 (76.9)	448 (77.8)	878 (77.4)
EBV Mismatch (Recipient/ Donor), n (%)	Negative/Negative	9 (1.6)	10 (1.7)	19 (1.7)
	Negative/Positive	24 (4.3)	29 (5.0)	53 (4.7)
	Negative/Unknown	11 (2.0)	16 (2.8)	27 (2.4)
	Positive/Negative	24 (4.3)	24 (4.2)	48 (4.2)
	Positive/Positive	256 (45.8)	264 (45.8)	520 (45.8)
	Positive/Unknown	150 (26.8)	160 (27.8)	310 (27.3)
	Unknown/Negative	3 (0.5)	2 (0.3)	5 (0.4)
	Unknown/Positive	26 (4.7)	22 (3.8)	48 (4.2)
ABO Blood type, n (%)	A	217 (39.0)	242 (42.0)	459 (40.5)
	AB	41 (7.4)	39 (6.8)	80 (7.1)
	B	79 (14.2)	78 (13.5)	157 (13.9)
	O	220 (39.5)	217 (37.7)	437 (38.6)
ABO Mismatch, n (%)	Identical†	528 (95.3)	547 (95.6)	1075 (95.5)
	Compatible‡	26 (4.7)	25 (4.4)	51 (4.5)

Table continues on next page

		Arm 1 (N = 561)	Arm 2 (N = 577)	Total (N = 1138)
HLA Type Mismatch, n (%)	A: 0	118 (21.7)	103 (18.4)	221 (20.0)
	A: 1	295 (54.1)	306 (54.7)	601 (54.4)
	A: 2	132 (24.2)	150 (26.8)	282 (25.5)
	Mean A	1.03	1.08	1.06
	B: 0	65 (11.9)	62 (11.0)	127 (11.5)
	B: 1	282 (51.7)	291 (51.7)	573 (51.7)
	B: 2	198 (36.3)	210 (37.3)	408 (36.8)
	Mean B	1.24	1.26	1.25
	DR: 0	155 (29.0)	179 (32.6)	334 (30.8)
	DR: 1	310 (58.1)	293 (53.4)	603 (55.7)
	DR: 2	69 (12.9)	77 (14.0)	146 (13.5)
	Mean DR	0.84	0.81	0.83
Total HLA Mismatch, n (%)	0	21 (3.8)	17 (3.0)	38 (3.4)
	1	38 (6.9)	34 (6.0)	72 (6.4)
	2	91 (16.4)	110 (19.3)	201 (17.9)
	3	180 (32.5)	167 (29.3)	347 (30.9)
	4	131 (23.6)	149 (26.1)	280 (24.9)
	5	82 (14.8)	69 (12.1)	151 (13.4)
	6	11 (2.0)	24 (4.2)	35 (3.1)
	Mean total HLA	3.18	3.23	3.20
PRA Grade	N	518	547	1065
	Mean (SD)	0.76 (2.62)	1.25 (3.91)	1.01 (3.35)
	Median (Min, Max)	0.0 (0.0, 20.0)	0.0 (0.0, 29.0)	0.0 (0.0, 29.0)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only)

BMI: body mass index; CMV: cytomegalovirus; EBV: Epstein Barr virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; PRA: panel reactive antibody

†: Recipient and donor have the same blood group.

‡ Compatible means that an A or B recipient can only receive an organ from a donor with the same blood group but as well receive an organ from an O donor or an AB recipient can also receive an organ from a O, A or B donor.

Lines for ‘not recorded’ and for ‘unknown’ or ‘unknown/unknown’ are not shown for readability. Full details are provided in the source tables.

Source: Tables 12.1.2.1.1, 12.1.4.1.1 and 12.1.4.2.1, 12.1.6.1

Table 2 Primary Diagnosis for Kidney Transplantation and Previous Transplant Information (SAF)

		Arm 1 (N = 561)	Arm 2 (N = 577)	Total (N = 1138)
Reason for kidney failure, n (%)	Glomerulonephritis	78 (13.9)	109 (18.9)	187 (16.4)
	Membranoproliferative glomerulonephritis	8 (1.4)	13 (2.3)	21 (1.8)
	Focal segmental glomerulonephritis	17 (3.0)	13 (2.3)	30 (2.6)
	Systemic lupus erythematosis	4 (0.7)	1 (0.2)	5 (0.4)
	Hemolytic uremic syndrome	2 (0.4)	3 (0.5)	5 (0.4)
	Hypertensive nephrosclerosis (including hypertensive nephropathy)	87 (15.5)	64 (11.1)	151 (13.3)
	Polycystic kidney disease	127 (22.6)	138 (24.0)	265 (23.3)
	Tubular and interstitial disease	40 (7.1)	31 (5.4)	71 (6.2)
	IgA nephropathy	55 (9.8)	54 (9.4)	109 (9.6)
	Obstructive uropathy (including chronic pyelonephritis)	33 (5.9)	36 (6.3)	69 (6.1)
	Hereditary nephropathy	22 (3.9)	24 (4.2)	46 (4.0)
	Unknown	59 (10.5)	61 (10.6)	120 (10.6)
	Other	29 (5.2)	29 (5.0)	58 (5.1)
	Not Recorded	0	1	1
Number of previous kidney transplants, n (%)	None	548 (97.7)	557 (96.5)	1105 (97.1)
	1	13 (2.3)	18 (3.1)	31 (2.7)
	2	0	2 (0.3)	2 (0.2)
Duration since last kidney transplant (Years)	N	13	20	33
	Mean (SD)	11.54 (6.85)	13.40 (7.63)	12.67 (7.28)
	Median (Min, Max)	11.0 (3.0, 24.0)	13.0 (1.0, 29.0)	13.0 (1.0, 29.0)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

Source: Table 12.1.8.1

Table 3 Kaplan-Meier Estimate of NODAT Rate and First ADA Criterion Met (FAS)

		Arm 1 (N = 528)	Arm 2 (N = 553)	Total (N = 1081)
Overall NODAT rate, n (%)	Week 2	18 (3.5)	13 (2.4)	31
	Week 4	30 (5.9)	19 (3.6)	49
	Week 8	40 (8.0)	38 (7.4)	78
	Week 12	59 (12.0)	50 (9.9)	109
	Week 24+ †	77 (17.4)	74 (16.6)	151
First ADA Criterion Met ‡, n (%):				
HbA1c ≥ 6.5% at or after the week 12 visit		15 (19.5)	15 (20.3)	30 (19.9)
FPG ≥ 126 mg/dL (7.0 mmol/L)		34 (44.2)	27 (36.5)	61 (40.4)
2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT		23 (29.9)	27 (36.5)	50 (33.1)
Symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L)		5 (6.5)	5 (6.8)	10 (6.6)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

ADA: American Diabetic Association; FAS: Full Analysis Set; FPG: fasting plasma glucose; HbA_{1c}: glycated hemoglobin; NODAT: new onset diabetes after transplantation; OGTT: oral glucose tolerance test.

† Events that happened at week 24 or after are grouped into the week 24+.

‡ In the event that multiple ADA criteria were met simultaneously, patients were counted under each criterion met.

Source: Tables 12.3.1.1 and 12.3.1.3.1

Table 4 Summary Results for Secondary Efficacy Variables Until Week 24† (ITT)

	Arm 1 N = 551 n (%)	Arm 2 N = 571 n (%)	Arm 1 – Arm 2 Kaplan-Meier Estimate (%)	95% CI (%)	P-value‡	Source Table
Efficacy Failure	133 (28.5)	154 (31.1)	2.6	-3.4, 8.6	0.1302	12.3.3.2.1.1
Efficacy Failure or NODAT	187 (38.7)	197 (38.8)	0.0	-6.3, 6.4	0.4415	12.3.3.1.1.1
Graft Loss	25 (4.8)	27 (5.0)	0.2	-2.4, 2.8	0.9028	12.3.3.2.2.1
Deaths (patient survival)	8 (1.6)	5 (1.0)	0.6	-2.0, 0.8	0.3344	12.3.3.2.3.1
Acute rejection §	94 (18.2)	141 (25.9)	7.7	2.7, 12.7	0.0012	12.3.3.3.1.1
BCAR	45 (8.7)	74 (13.6)	4.9	1.1, 8.6	0.0061	12.3.3.3.2.1
Corticosteroid-resistant AR †	23 (4.4)	30 (5.5)	1.1	-1.5, 3.7	0.3849	12.3.3.3.3.1
Corticosteroid-resistant BCAR	18 (3.4)	21 (3.8)	0.4	-1.9, 2.6	0.6880	12.3.3.3.4.1

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

Patients with no events were censored at the date of last evaluation or date of death, for patients who died or date of graft loss for patients with graft loss. For corticosteroid-resistant BCAR, patients with no events for the composite were censored at the date of last evaluation.

AR: acute rejection; BCAR: biopsy-confirmed acute rejection; CI: confidence interval; NODAT: new onset diabetes after transplantation

† Events that occurred at week 24 or after were grouped into week 24.

‡ From Wilcoxon Gehan test

§ Acute rejection by signs and symptoms

Table 5 Frequency of Types of Acute Rejections and Biopsy-Confirmed Acute Rejections Until Week 24 (ITT)

	Arm 1 N = 551		Arm 2 N = 571		Total N = 1122	
	n (%)	Episodes	n (%)	Episodes	n (%)	Episodes
AR by signs and symptoms						
Any acute rejection	94 (17.1%)	107	141 (24.7%)	165	235 (20.9%)	272
Spontaneously resolving AR †	10 (1.8%)	10	14 (2.5%)	16	24 (2.1%)	26
Corticosteroid sensitive AR‡	56 (10.2%)	64	94 (16.5%)	103	150 (13.4%)	167
Corticosteroid resistant AR §	23 (4.2%)	23	30 (5.3%)	31	53 (4.7%)	54
Other AR ††	8 (1.5%)	8	11 (1.9%)	11	19 (1.7%)	19
BCAR						
Any BCAR	45 (8.2%)	50	74 (13.0%)	84	119 (10.6%)	134
Spontaneously resolving BCAR †	1 (0.2%)	1	0	0	1 (0.1%)	1
Corticosteroid sensitive BCAR ‡	23 (4.2%)	26	49 (8.6%)	52	72 (6.4%)	78
Corticosteroid resistant BCAR ¶	18 (3.3%)	18	21 (3.7%)	22	39 (3.5%)	40
Other AR ††	3 (0.5%)	3	6 (1.1%)	6	9 (0.8%)	9

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).
Excluding acute rejection episodes during the follow-up.

AR: Acute rejection; BCAR: biopsy-confirmed acute reaction

† Rejection episode that was not treated with new or increased corticosteroid medication, antibodies or any medication and which resolved, irrespective of any Advagraf or MMF dose changes.

‡ Rejection treated with new or increased corticosteroid medication only and which resolved irrespective of any Advagraf or MMF dose changes.

§ Rejection episode which did not resolve following treatment with corticosteroids.

¶ Rejection episode which did not resolve following treatment with corticosteroids and was confirmed by biopsy.

†† All other acute rejections.

Source: Tables 12.3.3.3.5.1 and 12.3.3.3.6.1

Table 6 Renal Function at Week 24 (ITT)

Parameter†	Statistic	Arm 1	Arm 2	Arm 1 - Arm 2
Glomerular Filtration Rate (MDRD4) [mL/min/1.73m^2]	N	548	570	
	Mean (SD)	47.1 (21.32)	47.3 (22.43)	
	Median (Min, Max)	46.1 (0.0, 127.9)	47.4 (0.0, 141.7)	
	LS-Mean	47.1	47.3	-0.2
	95% CI			(-2.8, 2.4)
	P-value			0.875
Creatinine Clearance (Cockcroft-Gault) [mL/min]	N‡	456	472	
	Mean (SD)	53.8 (27.16)	51.7 (28.50)	
	Median (Min, Max)	54.0 (0.0, 158.4)	51.2 (0.0, 159.2)	
	LS-Mean	53.8	51.7	2.1
	95% CI			(-1.5, 5.7)
	P-value			0.247
Glomerular Filtration Rate (CKD-EPI) [mL/min/1.73m^2]	N	548	570	
	Mean (SD)	48.0 (22.61)	48.1 (23.40)	
	Median (Min, Max)	46.9 (0.0, 126.8)	47.9 (0.0, 118.3)	
	LS-Mean	48.0	48.1	-0.1
	95% CI			(-2.8, 2.6)
	P-value			0.940

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

† Week 24 is actually week 24 ± 2 weeks.

‡ N is lower due to missing values for body weight.

Source Table 12.3.3.4.2.1

Table 7 Summary of EuroQoL 5-Dimension Questionnaire at Baseline and Week 24 (ITT)

	Arm 1 (N = 551)			Arm 2 (N = 571)			Total (N = 1122)		
Score	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Mobility									
Baseline	461 (86.8%)	68 (12.8%)	2 (0.4%)	488 (87.9%)	66 (11.9%)	1 (0.2%)	949 (87.4%)	134 (12.3%)	3 (0.3%)
Week 24	400 (88.7%)	49 (10.9%)	2 (0.4%)	403 (86.1%)	62 (13.2%)	3 (0.6%)	803 (87.4%)	111 (12.1%)	5 (0.5%)
Self-Care									
Baseline	499 (93.8%)	31 (5.8%)	2 (0.4%)	529 (95.3%)	25 (4.5%)	1 (0.2%)	1028 (94.6%)	56 (5.2%)	3 (0.3%)
Week 24	439 (97.3%)	10 (2.2%)	2 (0.4%)	454 (97.0%)	12 (2.6%)	2 (0.4%)	893 (97.2%)	22 (2.4%)	4 (0.4%)
Usual Activities									
Baseline	403 (75.8%)	119 (22.4%)	10 (1.9%)	433 (78.0%)	115 (20.7%)	7 (1.3%)	836 (76.9%)	234 (21.5%)	17 (1.6%)
Week 24	395 (87.6%)	52 (11.5%)	4 (0.9%)	392 (83.8%)	73 (15.6%)	3 (0.6%)	787 (85.6%)	125 (13.6%)	7 (0.8%)
Pain/Discomfort									
Baseline	356 (66.9%)	172 (32.3%)	4 (0.8%)	382 (68.8%)	164 (29.5%)	9 (1.6%)	738 (67.9%)	336 (30.9%)	13 (1.2%)
Week 24	335 (74.3%)	109 (24.2%)	7 (1.6%)	348 (74.4%)	114 (24.4%)	6 (1.3%)	683 (74.3%)	223 (24.3%)	13 (1.4%)
Anxiety/Depression									
Baseline	348 (65.4%)	164 (30.8%)	20 (3.8%)	376 (67.7%)	161 (29.0%)	18 (3.2%)	724 (66.6%)	325 (29.9%)	38 (3.5%)
Week 24	371 (82.3%)	77 (17.1%)	3 (0.7%)	379 (81.0%)	82 (17.5%)	7 (1.5%)	750 (81.6%)	159 (17.3%)	10 (1.1%)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

The possible 5-dimension scores were: 1 (‘No problems’), 2 (‘moderate problem’) and 3 (‘Extremely bad’).

Source: Table 12.3.4.3.1

Table 8 Summary of Biomarkers of Kidney Injury by Treatment Arm and Efficacy Failure Subgroup at the End of the Study (ITT)

	Arm 1			Arm 2		
	Efficacy Failure (N = 133)	**No Efficacy Failure (N = 418)**	**Total (N = 551)**	**Efficacy Failure (N = 197)**	**No Efficacy Failure (N = 374)**	**Total (N = 571)**
MCP1 (pg/mL)						
N	107	410	517	184	365	549
Mean (SD)	432.0 (344.5)	300.9 (256.3)	328.0 (281.5)	437.7 (353.4)	313.7 (261.3)	355.2 (300.8)
Median	311.5	227.8	245	292.95	241.3	256.1
(Min, Max)	(12.5, 1049.0)	(12.5, 1049.0)	(12.5, 1049.0)	(12.5, 1049.0)	(12.5, 1049.0)	(12.5, 1049.0)
MCP1/UCR (ng/mmol)						
N	107	410	517	184	365	549
Mean (SD)	75.0 (98.9)	42.4 (43.2)	49.1 (60.5)	66.4 (61.0)	50.4 (144.1)	55.8 (122.9)
Median	46.7	28.2	30.8	45.5	30.5	34.4
(Min, Max)	(6.9, 874.2)	(3.2, 384.3)	(3.2, 874.2)	(3.4, 311.8)	(3.5, 2696.0)	(3.4, 2696.0)
IP10 (pg/mL)						
N	107	410	517	184	365	549
Mean (SD)	31.4 (54.2)	16.1 (18.2)	19.3 (30.1)	24.7 (38.5)	17.5 (23.9)	19.9 (29.8)
Median	10.0	7.8	7.8	9.35	7.8	7.8
(Min, Max)	(7.8, 387.1)	(7.8, 149.9)	(7.8, 387.1)	(7.8, 345.6)	(7.8, 291.7)	(7.8, 345.6)
IP10/UCR (ng/mmol)						
N	107	410	517	183	364	547
Mean (SD)	4.8 (8.0)	2.7 (3.9)	3.1 (5.1)	4.0 (5.3)	3.9 (26.5)	3.9 (21.9)
Median	2.2	1.5	1.7	2.0	1.5	1.6
(Min, Max)	(0.7, 67.9)	(0.4, 30.0)	(0.4, 67.9)	(0.4, 34.9)	(0.3, 506.0)	(0.3, 506.0)
UCREATQQ (mmol/L)						
N	107	410	517	184	365	549
Mean (SD)	6.9 (3.5)	8.3 (4.9)	8.0 (4.6)	7.6 (4.4)	8.0 (4.1)	7.9 (4.2)
Median	6.5	7.25	7.0	6.9	7.5	7.3
(Min, Max)	(1.2, 20.5)	(0.3, 29.3)	(0.3, 29.3)	(0.4, 27.6)	(0.1, 24.4)	(0.1, 27.6)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

MCP1: monocyte chemoattractant protein 1; IP10: interferon gamma-induced protein 10;
UCR: urine creatinine ratio; UCREATQQ: urine creatinine quantitative.

Source: Tables 12.3.4.1.1, 12.3.4.1.2 and 12.3.4.1.3

Table 9 Summary of Adverse Events (SAF)

		Arm 1 (N = 561)	**Arm 2 (N = 577)**	**Total (N = 1138)**
N (%) with any TEAE		508 (90.6)	530 (91.9)	1038 (91.2)
Total TEAEs		4296	4682	8978
N (%) with treatment-related† TEAEs		322 (57.4)	342 (59.3)	664 (58.3)
Total treatment-related TEAEs		874	998	1872
N (%) deaths‡		8 (1.4)	5 (0.9)	13 (1.1)
N (%) deaths until withdrawal		6 (1.1)	1 (0.2)	7 (0.6)
N (%) deaths after withdrawal (occurred during follow-up)		2 (0.4)	4 (0.7)	6 (0.5)
N (%) with serious TEAEs		263 (46.9)	262 (45.4)	525 (46.1)
Total serious TEAEs		492	488	980
N (%) with treatment-related serious TEAEs: Advagraf		106 (18.9)	107 (18.5)	213 (18.7)
Total treatment-related[#] serious TEAEs		160	152	312
N (%) with treatment -related serious TEAEs: MMF		76 (13.5)	90 (15.6)	166 (14.6)
Total treatment-related serious TEAEs		115	130	245
N (%) with treatment -related serious TEAEs: Basiliximab		17 (3.0)	13 (2.3)	30 (2.6)
Total treatment-related serious TEAEs		28	18	46
N (%) with treatment -related serious TEAEs: Corticosteroids		28 (5.0)	21 (3.6)	49 (4.3)
Total treatment-related serious TEAEs		42	34	76
N (%) discontinued due to TEAE§		46 (8.2)	44 (7.6)	90 (7.9)
Total TEAEs leading to discontinuation		58	58	116
N (%) discontinued due to treatment-related TEAE		20 (3.6)	24 (4.2)	44 (3.9)
Total treatment-related[#] TEAEs leading to discontinuation		23	31	54
N (%) with TEAE by severity	Mild	124 (22.1)	116 (20.1)	240 (21.1)
	Moderate	258 (46.0)	285 (49.4)	543 (47.7)
	Severe	126 (22.5)	129 (22.4)	255 (22.4)

Arm 1: Advagraf + Basiliximab + MMF + Steroids (discontinued at 10 days);
Arm 2: Advagraf + Basiliximab + MMF + Steroids (optional intra-op bolus only).

TEAE: treatment-emergent adverse event.

† Adverse events that are possibly or probably related to treatment, or for which the relationship is missing.

‡ Only AEs with outcome 'fatal' are counted.

§ Only AEs that were the primary reason for discontinuation are taken into account.

Source: Tables 12.6.1.1 and 12.6.1.8