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

SYNOPSIS

Title of Study: A Multicenter, Three Arm, Randomized, Open Label Clinical Study to Compare Renal Function in Liver Transplant Recipients Receiving an Immunosuppressive Regimen of Advagraf® (Immediately or Delayed Post-transplant) and MMF with or without a Monoclonal Anti-IL2R Antibody (Basiliximab)

Investigators/Coordinating Investigator: Dr. [redacted]

Study Centers: This multinational study was conducted at 72 sites in 23 European and non-European countries.

Publication Based on the Study: No publications based on the results of this study were available as of the time of finalization of this report.

Study Period: September 2009 to January 2013

Study Initiation Date (Date of First Enrollment): September 30, 2009

Study Completion Date (Date of Last Evaluation): January 4, 2013

Phase of Development: Phase 3b

Objectives: The primary objective of this study was to compare the 3 therapy regimens with regard to renal function (arms 2 and 3 each being compared with arm 1).

The secondary objective was to compare the safety and efficacy profiles of the 3 therapy regimens with each other.

Methodology: Study PMR-EC-1107 (DIAMOND France study) was organized as a substudy of Study PMR-EC-1106 (DIAMOND study). Study PMR-EC-1107 was conducted in French centers only (14 sites). The French ethics committee requested descriptive changes in the rationale of the study and required this to be submitted under a new EudraCT number. Operational details of the Study PMR-EC-1106 protocol were not changed and therefore, the data from Study PMR-EC-1107 has been analyzed with Study PMR-EC-1106. The database was a single database and included all available data from both Studies PMR-EC-1106 and PMR-EC-1107.

This study was a multicenter, randomized, open-label, 3-arm, parallel group, comparative, phase 3b study. Patients about to undergo liver allograft transplantation were randomized to one of the following treatment arms (with administration of corticosteroids being optional):

Arm 1: Advagraf + mycophenolate mofetil (MMF) + corticosteroids (bolus)

Arm 2: Advagraf + MMF + basiliximab + corticosteroids (bolus)

Arm 3: Advagraf (5 days delay) + MMF + basiliximab + corticosteroids (bolus)

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The randomization was 1:1:1 stratified by hepatitis C virus (HCV) status of the patient. Arm 1 served as the reference arm for the study. Arm 2 (lower tacrolimus exposure) and arm 3 (delayed Advagraf administration) were each compared separately to arm 1.

The Investigational Medicinal Products (IMPs) Advagraf and basiliximab were provided by the Sponsor. MMF and iohexol although not considered as IMPs in this study were also provided. Corticosteroids were not provided by the Sponsor and also were not considered to be IMPs.

Baseline assessments were performed at visit 1, within 4 days prior to surgery (laboratory assessments must have been completed within 48 hours prior to surgery [day 0]). Some assessments (e.g., viral testing) were taken from records prior to this. The first dose of Advagraf was ideally administered in the morning following the liver transplantation procedure, but in any case, within 18 hours of skin closure. The treatment period lasted for 24 weeks after transplantation.

Number of Patients (Planned, Enrolled and Analyzed): In order to reach 269 evaluable patients per arm (Per Protocol Set [PPS]) it was planned to enroll 900 patients (300 per arm, 8 - 48 patients per center) into global Study PMR-EC-1106, of which approximately 150 patients were planned to be enrolled into Study PMR-EC-1107 (French centers only). Of 901 patients screened, 893 were randomized to receive treatment and 857 underwent transplantation and received at least one dose of study medication (Advagraf or basiliximab) and were thus eligible for the Safety Analysis Set (SAF). A total of 844 (94.5%) patients were included in the Full Analysis Set (FAS) and 643 (72.0%) patients were included in the PPS.

Diagnosis and Main Criteria for Inclusion: Patients at least 18 years of age undergoing orthotopic liver or split liver allograft transplantation who provided informed consent and to whom all of the inclusion and none of the exclusion criteria applied, were eligible for inclusion in this study.

Test Product, Dose and Mode of Administration, Batch Numbers: The protocol-specified treatments for this study are summarized as follows. Advagraf was available as hard gelatin capsules with 0.5 mg, 1 mg and 5 mg of tacrolimus. In the United States, Advagraf is named Astagraf XL™ (tacrolimus extended-release capsules). The initial dose of Advagraf in arm 1 was 0.2 mg/kg per day given orally in one dose. After the initial dose, subsequent Advagraf doses were taken orally once a day only in the morning, and doses were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events (AEs) and observing the following recommended whole blood trough level ranges: days 0 to 42: 5 to 15 ng/mL, days 43 to 168: 5 to 12 ng/mL.

The initial dose of Advagraf in arm 2 was 0.15 to 0.175 mg/kg per day given orally in one dose. On day 2, the dose was 0.1 mg/kg per day administered orally in one dose. After the initial dose, subsequent Advagraf doses were taken orally once a day only in the morning, and doses were adjusted on the basis of clinical evidence of efficacy, occurrence of AEs and observing the following recommended whole blood trough level ranges: days 0 to 42: 5 to 15 ng/mL. At day 43, provided the patient had not received treatment for an acute rejection episode and the last tacrolimus blood trough level was ≥ 5 ng/mL, a dose reduction of 20 to 25% was to be made, and

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subsequent doses adjusted on the basis of clinical evidence of efficacy, occurrence of AEs and observing the following recommended whole blood trough ranges: days 43 to 168: 4 to 12 ng/mL.

The initial dose of Advagraf in arm 3 was 0.2 mg/kg per day administered orally once a day only in the morning. The first dose was administered 5 days after the liver transplantation procedure. After the initial dose, subsequent Advagraf doses were taken orally once a day only in the morning, and doses were adjusted on the basis of clinical evidence of efficacy, occurrence of AEs and observing the following recommended whole blood trough level ranges: days 5 to 42: 5 to 15 ng/mL, days 43 to 168: 5 to 12 ng/mL.

MMF was available as 500 mg ampules for infusion and 250 mg capsules. The first postoperative dose of MMF (1 g) was administered intravenously within 12 hours following skin closure. Postoperative dosing was to be given intravenously 2 g/day split in 2 doses of 1 g for 3 to 5 days posttransplant, after which dosing followed orally until day 14, with 2 g/day orally split in 2 doses of 1 g and thereafter a recommended maintenance dose of 1 g/day orally split in 2 doses of 0.5 g. At the physician's discretion, oral dosing could have commenced at 3 g/day until day 14, split in 2 doses of 1.5 g/day, and thereafter a recommended maintenance dose of 1.5 g/day orally, split in 2 doses of 0.75 g.

Basiliximab was available as 20 mg ampules for infusion. Only 2 doses of basiliximab (in arms 2 and 3) were given: day 0: 20 mg administered during the transplant procedure when hemostasis was secured or immediately posttransplant; day 4: 20 mg. No basiliximab dose modification was permitted.

The batch numbers are provided in Appendix 13.1.6.

Duration of Treatment (or Duration of Study, if applicable): The treatment period lasted for 24 weeks after transplantation.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable.

Criteria for Evaluation: The primary efficacy variable of glomerular filtration rate (GFR) was estimated using the Modification Diet in Renal Disease 4 (MDRD4) formula at 24 weeks after transplantation.

The secondary efficacy variables were:

- Efficacy failure, which was defined in this study as graft loss (defined as retransplantation or death) or BCAR:
    - Incidence of and time to first incidence of the composite event: graft loss (defined as retransplantation or death) or BCAR
- Efficacy failure or early withdrawal
    - Incidence of and time to first incidence of the composite event: graft loss (defined as retransplantation or death) or BCAR or early withdrawal (last evaluation is prior to day 138)
- Renal function:
    - GFR at 24 weeks after transplantation measured by iohexol clearance

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  - GFR at 24 weeks after transplantation estimated using a cystatin C based formula
  - Creatinine clearance at 24 weeks (estimated using Cockcroft and Gault)
  - Estimated GFR (using MDRD4 formula) at each scheduled visit
- Acute rejections:
  - Incidence of and time to first incidence of acute rejection
  - Incidence of and time to first incidence of corticosteroid-resistant acute rejection
  - Overall frequency of acute rejection episodes
- Biopsy-confirmed acute rejections:
  - Incidence of and time to first incidence of BCAR
  - Incidence of and time to first incidence of biopsy-confirmed corticosteroid-resistant acute rejection
  - Overall frequency of BCAR episodes
  - Severity of BCAR episodes

The safety variables for this study included:

- Patient and graft survival
- Incidence of AEs
- Incidence of AEs of special interest (diabetes mellitus, neurological disorders, hypertension, vascular disorders, malignancies, posttransplant lymphoproliferative disorder, cytomegalovirus [CMV] infection, Epstein-Barr virus [EBV] infection)
- Laboratory parameters (hematology, biochemistry and urinalysis)
- Vital signs (systolic and diastolic blood pressure and pulse rate)

Statistical Methods: All statistical comparisons were made using 2-sided tests at the $\alpha = 0.05$ significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were 2-sided. All data processing, summarization and analyses were performed using Statistical Analytical System (SAS®) Version 9.1.3 or higher; some programs were created on Windows and the final runs were all on UNIX.

The FAS included all patients who were enrolled in the study and were randomized, transplanted and received at least one dose of study medication (Advagraf, basiliximab or MMF). Patients in the FAS population were analyzed for the primary variable according to their randomized treatment even if a mistake was made and the patient did not receive their treatment assigned at randomization. The PPS included all patients from the FAS who did not have any PPS violations. PPS violations included violation of relevant inclusion/exclusion criteria, deviation from protocol compliant administration and use of prohibited concomitant medication. Patients were analyzed for the primary variable in the PPS population according to their received treatment. The SAF consisted of all patients who were transplanted (i.e., underwent reperfusion; identified by those in the electronic CRF [eCRF] with a date of reperfusion). The SAF used the actual treatment, as recorded by the investigator in

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the eCRF, if this differed from the randomized treatment. The Modified Intent-to-treat (ITT) Analysis Set was the same as the SAF.

The primary variable of the study was GFR at 24 weeks after transplantation estimated using the MDRD4 formula. Arms 2 and 3 were compared and tested for noninferiority of mean GFR versus the GFR of arm 1. The primary analysis was carried out using the PPS and the FAS for noninferiority, and using the FAS for superiority (once noninferiority was established).

The null and alternative hypotheses were:

$$H_{0i}: \mu_{ti} \leq \mu_r - \Delta, H_{1i}: \mu_{ti} > \mu_r - \Delta,$$

here μ_{ti} (i = 2, 3) denotes mean in arms 2 and 3 and μ_r denotes mean in arm 1. The noninferiority margin Δ was 6 mL/min/1.73 m^2.

Analysis of covariance (ANCOVA) with Dunnett's adjustment for multiplicity was used for primary endpoint testing. GFR was modeled as a function of treatment group, pooled site, sex, race (black) and HCV status as fixed factors and the baseline value as covariate.

Least square (LS) means from the ANCOVA for each treatment arm (adjusted for the covariates), LS means for differences between each treatment arm, Dunnett's P values, standard errors and 95% CIs for those differences were presented (CIs for arms 2 and 3 vs arm 1 used Dunnett's adjustment for multiplicity).

H_{0i} was to be rejected and noninferiority shown if the lower bound of the Dunnett's 2-sided 95% CI for the differences in GFR values was above - Δ for both the FAS and the PPS. If noninferiority could be shown in arm 2 or arm 3, then a test for superiority for that arm was to be performed in accordance with the Committee for Proprietary Medicinal Product (CPMP) "Points to consider on switching between superiority and non-inferiority, 27 July 2000" still using Dunnett's adjustment, but without further adjustment of the level of significance. Superiority was to be shown if the Dunnett's 2-sided 95% CI for the treatment differences in mean GFR values was above zero. The primary analysis set for the superiority test was the FAS.

ANCOVA results were validated by producing plots of residuals versus fitted values and plots of ordered residuals versus normal order scores. If either of these showed serious deviations from underlying assumptions, then further exploratory analyses were to be done to investigate the robustness of the results. In such cases, as an alternative to ANCOVA, van Elteren's test stratifying by center/region and HCV status of the recipient (Cochran-Mantel-Haenszel [CMH] using the SCORES=MODRIDIT option in SAS) was to be used.

The primary comparison was for arms 2 and 3 versus arm 1, as described above. Dunnett's test was used to adjust statistical significance for comparisons of arms 2 and 3 with arm 1, for all measures of renal function. Therefore, arms 2 and 3 were compared with arm 1 without affecting the overall type 1 error.

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The study was designed to test for noninferiority using both the FAS and PPS. If noninferiority was shown for both FAS and PPS, then the study could test for superiority without further adjustments and without affecting the overall type 1 error. Superiority was tested using the FAS as this is the recommended population, generally more conservative, and avoids questions of multiplicity for superiority between populations. As defined a priori (in the SAP), superiority testing used the FAS. For superiority, the analysis of the primary variable using the PPS was supporting (a sensitivity analysis).

The primary analysis was repeated (including Dunnett's adjustment for comparisons with arm 1) as follows:

- Using pooled country in place of pooled site for the FAS and PPS
- A potential center/region-by-treatment interaction effect was investigated in a further exploratory analysis through ANCOVA with the model in the primary analysis and the addition of pooled site-by-treatment interaction. If the interaction was significant, extended exploratory analyses were to be performed to clarify the reason and LS means were to be presented so as to give a full account of treatment differences.
- A potential HCV status-by-treatment interaction effect was investigated in a further exploratory analysis through ANCOVA using the model in the primary analysis and the addition of HCV status-by-treatment interaction. If the interaction was significant, extended exploratory analyses were to be performed to clarify the reason and LS means were to be presented so as to give a full account of treatment differences.
- If a major imbalance in any baseline variable was found for the FAS, a supplementary analysis of the primary efficacy endpoint was to be made adding that baseline variable as an extra covariate. This would explore the robustness of the main result to the presence or absence of the imbalance.

In order to explore the possibility that the effect of treatment might be different in different subgroups, a potential subgroup-by-treatment interaction effect was investigated in a further exploratory analysis using ANCOVA with treatment group, subgroup and subgroup-by-treatment interaction.

Further exploratory comparison of the primary endpoint between the Advagraf treatment groups (arms 2 and 3) was performed using the same model as the primary analysis. Due to the explorative nature of analysis, no alpha adjustment was needed.

All secondary endpoints were summarized per treatment group using appropriate descriptive statistics (i.e., number [%] of patients for categorical variables and mean, SD, median, minimum and maximum for continuous variables). Where appropriate, summaries were provided over time. Secondary variables were analyzed in a descriptive manner. Statistical comparisons for secondary endpoints were done among the 3 treatment arms using 2-sided descriptive P values and 95% CIs. As these are descriptive, Dunnett's correction was not used.

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The following were analyzed in the same manner as the primary analysis for the primary variable, using the FAS:

- GFR at 24 weeks after transplantation measured by iohexol clearance
- GFR at 24 weeks after transplantation estimated using cystatin C
- GFR at 24 weeks after transplantation estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
- Creatinine clearance at 24 weeks after transplantation estimated using the Cockcroft and Gault formula.

The following endpoints were analyzed using Kaplan-Meier procedures. The Wilcoxon-Gehan test was used for comparison of the survival functions in the 3 treatment groups (pairwise comparisons). In addition, 95% CIs for the Kaplan-Meier rates at each time point (normal approximation with the estimates of standard error according to Greenwood's formula) were presented. All time-to-event related parameters were analyzed relative to the day of skin closure, using the Modified ITT Analysis Set:

- Efficacy failure rate (censored on date of last evaluation),
- Graft survival (graft loss) (censored on date of last evaluation),
- Patient survival (censored on date of last evaluation),
- Acute rejection (censored on date of withdrawal or end of the study),
- BCAR (censored on date of withdrawal or end of the study),
- Corticosteroid-resistant acute rejection (censored on date of withdrawal or end of the study),
- Biopsy-confirmed corticosteroid-resistant acute rejection (censored on date of withdrawal or end of the study)

Patient Reported Outcome (EQ5D) was summarized using descriptive statistics, using the Modified ITT Analysis Set.

Safety analyses were performed on the SAF. Frequency tabulations were presented for all safety and tolerability data using descriptive statistics. In addition to the safety variables, routine clinical laboratory results and vital sign measurements were described. Selected safety analyses were repeated for subgroups based on sex, age (< 50 years, ≥ 50 years) and donor status (cadaveric, noncadaveric).

AEs as well as AEs of special interest were coded using MedDRA version 11.1. Frequency tabulations were presented for all safety and tolerability data using descriptive statistics.

Summary of Results/Conclusions:

Population: Of 901 patients screened, 893 were randomized and 857 underwent transplantation and were thus eligible for the SAF [Table 1]. In general, patients were analyzed according to their actual treatment. The main difference between the planned treatment and the actual treatment received was that 6 patients who were randomized to arm 1 received basiliximab perioperatively. For the analyses by the actual treatment, these

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patients were assigned to arm 2. For one patient who was randomized to arm 2, Advagraf was delayed. For analyses by actual treatment, this patient was assigned to arm 3. The primary variable of this study (GFR at week 24 estimated by the MDRD4 formula) has been analyzed using both the actual and the randomized treatment. For patients to be in the PPS, the actual treatment and the randomized treatment must have been the same. A total of 844 (94.5%) patients were included in the FAS and 643 (72.0%) patients were included in the PPS. Thirteen patients who were included in the SAF were excluded from the FAS because they did not receive study drug. The most common reason for exclusion from the PPS was that the patient withdrew prior to week 20 and did not have ongoing dialysis.

Demographic characteristics were similar across the 3 treatment arms [Table 2]. Approximately 70% of patients in the SAF were male and over 94% were white. Most patients (64.5%) were between 50 and 65 years of age, inclusive. Only 8.5% of patients were > 65 years of age.

Study Drug Exposure:

Advagraf: In the SAF, the results showed that the mean starting dose in arm 2 (0.13 mg/kg) was lower than arm 1 (0.17 mg/kg), which was expected based on the study design (starting Advagraf dose was 0.2 mg/kg in arms 1 and 3, 0.15-0.175 mg/kg in arm 2). The mean doses for arms 1 and 2 were similar starting from day 7 onward (range of 0.09-0.13 mg/kg and 0.10-0.13 mg/kg, respectively, from days 7-168). Arm 3 had a slightly higher mean Advagraf dose at day 7 (0.14 mg/kg compared to 0.10 mg/kg in both arms 1 and 2), but this was similar to the other arms by days 14 to 28 (0.13 mg/kg, 0.12-0.13 mg/kg and 0.13-0.14 mg/kg in arms 1, 2 and 3, respectively). All 3 treatment arms showed similar reductions in mean dose (mg/kg) from day 28 through day 168 (0.13 mg/kg on day 28 to 0.09 mg/kg on day 168 in arms 1 and 3 and 0.13 mg/kg on day 28 to 0.10 mg/kg on day 168 in arm 2). All 3 treatment arms showed an approximately 20% dose reduction between days 28 and 84 (the visits before and after day 42; mean of 0.13 mg/kg on day 28 to 0.11 mg/kg on day 84 in all 3 treatment arms). Therefore, the observed differences between the treatment arms were observed in the first 7 days of treatment. The number of patients was lowest at day 168 due to patient withdrawals. The EOS data included the last observation for patients, regardless of how long the patients participated in the study.

The doses of Advagraf were numerically higher in female patients compared with male patients by day 28 and remained higher for female patients through the end of the study. For male and female patients, the mean (mg/kg) starting doses in arm 2 in the SAF (0.13 mg/kg for both male and female patients) were lower than arm 1 (0.17 mg/kg for male and 0.18 mg/kg for female patients), which was expected based on the study design. The mean doses of Advagraf in arms 1 and 2 were similar from day 7 through the remainder of the study in both male (range of 0.08-0.12 mg/kg in arm 1 and 0.08-0.13 mg/kg in arm 2) and female (range of 0.12-0.15 mg/kg in arm 1 and 0.09-0.15 mg/kg in arm 2) patients. Arm 3 had a numerically higher mean Advagraf dose at day 7 compared with the other treatment arms in both male (0.14 mg/kg) and female (0.15 mg/kg) patients, but then the daily Advagraf dose for arm 3 was similar to the other arms by day 28 (0.13 mg/kg in male patients, 0.14 mg/kg in female patients).

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Exposure to tacrolimus was also assessed using tacrolimus whole blood trough level measurements and these were used as a rough guide to assess patient compliance. In the early period following initiation at 2 different doses (0.2 mg/kg in arms 1 and 3, 0.15-0.175 mg/kg in arm 2) and delayed Advagraf administration in arm 3, whole blood tacrolimus trough levels were generally numerically higher in arm 1 until day 14 and in both arms 1 and 3 until day 28; however, throughout the remainder of the study, whole blood tacrolimus trough levels were similar for the 3 treatment arms in the SAF, FAS and PPS. Per the protocol, until day 42 (visit 6), target trough levels were 5 to 15 ng/mL in all treatment arms. After day 42, target trough levels varied by arm (5-12 ng/mL in arms 1 and 3, 4-12 ng/mL in arm 2). The majority of patients had a whole blood trough level between 5 and 15 ng/mL throughout the study. The mean whole blood trough levels were 8.0, 8.2 and 7.8 ng/mL in arms 1, 2 and 3, respectively at day 168 (week 24) in the SAF.

Whole blood tacrolimus trough levels were similar between male and female patients within each treatment arm throughout the study (for male and female patients, respectively, in the SAF, range of 8.2-11.3 ng/mL and 7.5-11.6 ng/mL in arm 1 [starting on day 1], 7.3-9.0 ng/mL and 7.4-9.3 ng/mL in arm 2 [starting on day 1] and 8.1-10.5 ng/mL and 7.3-9.2 ng/mL in arm 3 [starting on day 7]). The mean whole blood trough levels were 8.2, 8.2 and 8.1 ng/mL in male patients arms 1, 2 and 3, respectively and 7.5, 8.3 and 7.3 ng/mL in female patients in arms 1, 2 and 3, respectively at day 168 (week 24) in the SAF.

MMF: The actual median daily doses of MMF followed the protocol-defined schedule. The median daily doses of MMF were the same in all 3 treatment arms at every visit throughout the study. The majority of patients received > 0 and ≤ 1.5 g/day of MMF on day 0, > 1.5 and < 2.5 g/day of MMF on days 1 to 14 and > 0 and ≤ 1.5 g/day of MMF on day 15 through the end of the study.

Corticosteroids: The median cumulative total dose of steroids (mg of prednisolone equivalents) was 625 mg and the median number of days treated was 1 day in all 3 treatment arms. The proportion of patients in the SAF without corticosteroid treatment for acute rejection was highest in arm 2 (90.7%) compared with arms 1 and 3 (85.5% and 85.9%, respectively) and the median number of days of corticosteroid treatment for acute rejection was numerically higher in arm 3 (6 days) compared with arms 1 and 2 (3 days each).

Basiliximab: As expected per the protocol, the median total basiliximab dose for the whole study was 40 mg. The majority of patients in the SAF (266 [91.4%] patients in arm 2 and 260 [93.9%] patients in arm 3) received both doses of basiliximab.

Efficacy Results: The primary objective of the study was to compare the 3 therapy regimens with regard to renal function, which was assessed by the GFR at 24 weeks after transplantation using the MDRD4 formula (mL/min/1.73 m^2). The study allowed testing for superiority since noninferiority was met for both arms 1 and 2.

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Superiority Testing

The LS mean GFR values at 24 weeks after transplantation using the MDRD4 formula were statistically significantly ($P < 0.05$) higher for arms 2 and 3 compared with arm 1 in the FAS when using either the planned ($P < 0.001$ for arm 2 compared with arm 1; $P = 0.034$ for arm 3 compared with arm 1) or the actual ($P = 0.001$ for arm 2 compared with arm 1; $P = 0.047$ for arm 3 compared with arm 1) treatment [Table 3]. The LS mean GFR values for arm 2 were numerically higher compared with arm 3 when using either the planned or actual treatment, but the differences were not statistically significant ($P = 0.131$ for the planned treatment; $P = 0.230$ for the actual treatment). The results for the PPS are supportive of the conclusions of the primary analysis for the FAS, though the size of the effect was not as large and the results were not statistically significant between treatment arms. The results of the sensitivity analyses support the results of the primary analysis.

Noninferiority Testing

The protocol specified to test for noninferiority of arms 2 and 3 against arm 1, with a noninferiority limit of 6 mL/min/1.73 m^2 (i.e., arms 2 and 3 are not more than 6 mL/min/1.73 m^2 worse than arm 1; the lower bound of the 95% confidence interval is greater than -6, no worse than -6). This was to be satisfied for FAS and PPS populations. The primary analysis was for the planned treatment (for the PPS, the planned treatment is the same as the actual treatment). The test for noninferiority was met as shown by the 95% confidence intervals described below (mL/min/1.73 m^2):

Arm 2 versus Arm 1:

- Using the PPS the 95% CI is (-1.0, 10.1), so arm 2 is no more than 1.0 worse than arm 1
- Using the FAS the 95% CI is (4.4, 16.0), so arm 2 is at least 4.4 better than arm 1

Arm 3 versus Arm 1:

- Using the PPS the 95% CI is (-1.1, 10.0), so arm 3 is no more than 1.1 worse than arm 1
- Using the FAS the 95% CI is (4.4, 16.0), so arm 3 is at least 4.4 better than arm 1

Based on the above results, it was concluded that arms 2 and 3 are noninferior to arm 1.

Secondary Efficacy Analyses

The results of the secondary efficacy analyses support the conclusions of the primary analysis. There were no statistically significant ($P < 0.05$) differences between treatment arms in efficacy failure rates in the Modified ITT Analysis Set, though the percentage of patients free from efficacy failure was numerically higher in arm 2 (77.6%) compared with arms 1 (72.0%) and 3 (73.9%).

Using the secondary measures to compare renal function between the treatment arms (GFR at 24 weeks estimated using the CKD-EPI formula, creatinine clearance at 24 weeks and GFR at 24 weeks estimated using

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cystatin C), patients from the FAS in arm 2 were found to have better renal function compared with patients in arm 1 [Table 4]. The unit of measure was mL/min/1.73 m^2 for all GFR analyses and mL/min for creatinine clearance. These differences were statistically significant for creatinine clearance ($P < 0.001$) and GFR estimated using the CKD-EPI formula ($P = 0.002$). Patients in arm 3 were also found to have better renal function compared with patients in arm 1. These differences were statistically significant for GFR estimated using the CKD-EPI formula ($P = 0.046$) and approaching statistical significance for creatinine clearance ($P = 0.071$). The results for GFR at 24 weeks estimated using cystatin C in the FAS were based on fewer patients, as this test was only done at the end of the study, and was often omitted at early withdrawal. The results for cystatin C were similar to the other renal function results, with the estimated GFR being numerically higher in arms 2 and 3 compared with arm 1, but these differences were not statistically significant ($P = 0.268$ for arm 2 compared with arm 1; $P = 0.256$ for arm 3 compared with arm 1; $P = 0.972$ for arm 2 compared with arm 3). The GFR at 24 weeks estimated using iohexol clearance in the FAS was similar between treatment arms.

The frequency of acute rejection was numerically lower in arm 2 (12.4%) compared with arms 1 and 3 (18.0% and 18.4%, respectively). In the Kaplan-Meier analysis of the rate of acute rejection over time, there were statistically significant differences between arm 2 and arm 1 and between arm 2 and arm 3 ($P = 0.0249$ and $P = 0.0192$, respectively; Wilcoxon-Gehan test), with more patients in arm 2 free from acute rejection compared with arms 1 and 3. In the Kaplan-Meier analysis of the rate of BCAR over time, there were statistically significant differences between arm 2 and arm 1 and between arm 2 and arm 3 ($P = 0.0164$ and $P = 0.0392$, respectively; Wilcoxon-Gehan test), with more patients in arm 2 free from BCAR compared with arms 1 and 3. These differences between treatment arms in the rates of acute rejection and BCAR were particularly noticeable in the first 2 weeks after transplantation.

Patient and graft survival rates were similar across all 3 treatment arms, with no statistically significant differences. The Kaplan-Meier estimated patient survival rates were 89.3%, 89.1% and 90.4% in arms 1, 2 and 3, respectively, at week 24 in the Modified ITT Analysis Set. The Kaplan-Meier estimated graft survival rates were 86.5%, 87.7% and 88.6% in arms 1, 2 and 3, respectively, at week 24 in the Modified ITT Analysis Set. Analyses of male and female outcomes were similar with no discernible difference between the genders.

The changes from baseline in health-related quality of life using the EQ5D were similar between treatment arms at week 24 in the Modified ITT Analysis Set, with all treatment arms showing an increase in quality of life compared to baseline. The percentage of patients who were on dialysis at the end of the study was 8.0%, 6.5% and 5.1% in arms 1, 2 and 3, respectively. The mean total number of days on dialysis was 4.66 days in arm 1, 2.87 days in arm 2 and 1.38 days in arm 3 in the Modified ITT Analysis Set. The mean number of days per patient with rejection was 3.37 days in arm 1, 2.47 days in arm 2 and 3.60 days in arm 3 in the Modified ITT Analysis Set. The percentage of patients who had no rejection episodes was 81.3%, 86.6% and 80.5% in arms 1, 2 and 3, respectively.

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

Safety Results: The 3 treatment arms in this study had similar safety profiles, with the proportion of patients reporting treatment-emergent adverse events (TEAEs) being similar between treatment arms (96.5%, 98.6% and 99.3% of patients in arms 1, 2 and 3, respectively). TEAEs reported by ≥ 20.0% of patients in any treatment arm were anemia, diarrhea, hypertension, renal failure, pleural effusion and nausea [Table 5]. The proportion of patients with individual common TEAEs was similar between treatment arms.

The proportion of patients with drug-related TEAEs was 77.2%, 79.0% and 71.8% in arms 1, 2 and 3, respectively. Study drug-related TEAEs reported by ≥ 10.0% of patients in any treatment arm were renal failure, diarrhea, hypertension and tremor. The proportion of patients with individual drug-related TEAEs was generally similar between treatment arms.

A total of 379 [44.2%] patients reported TEAEs of moderate maximum intensity and 362 [42.2%] patients reported TEAEs of severe maximum intensity. The percentage of patients who experienced severe TEAEs was 45.0% in arm 1, 44.0% in arm 2 and 37.5% in arm 3. Severe TEAEs reported by ≥ 2.0% of patients in any treatment arm were renal failure, acute renal failure, respiratory failure, complications of transplanted liver, pneumonia, sepsis, liver transplant rejection, postprocedural hemorrhage, pleural effusion, septic shock and transplant failure. The majority of events (51.9%) were mild in severity (4859/9367 events).

A total of 44 (5.1%) patients died during the study before early withdrawal or the end of the study. An additional 45 patients died between early withdrawal and the 24-week follow-up, for a total of 89 (10.4%) deaths overall. Of the deaths that occurred after early withdrawal/end-of-study, 15 were recorded as the outcome of TEAEs, for a total of 59 deaths associated with TEAEs. Three additional patients died more than 30 days after the 24-week follow-up visit, with mortality information reported in the Astellas safety database (malignant recurrent hepatic neoplasm [considered by the investigator to be unrelated to study medication], chronic renal failure [considered by the investigator to be probably related to study medication] and malignant neoplasm of pleura [considered by the investigator to be unrelated to study medication]). Of the 59 patients who had deaths associated with TEAEs, 16 (5.5%), 24 (8.2%) and 19 (6.9%) patients were in arms 1, 2 and 3, respectively. The 3 most common TEAEs with a fatal outcome were multi-organ failure, sepsis and septic shock. One death was considered to be probably related to study medication (poliorganic failure). A total of 14 deaths were considered by the investigator as being possibly related to study medication. All other deaths were considered to be unrelated to study medication.

The proportion of patients who reported a serious TEAE (including deaths) was 65.4%, 59.8% and 63.9% in arms 1, 2 and 3, respectively. Serious TEAEs (including deaths) reported by ≥ 4.0% of patients in any treatment arm were liver transplant rejection, renal failure, acute renal failure, respiratory failure and bile duct stenosis [Table 6].

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

The proportion of patients who reported a TEAE leading to permanent discontinuation of study drug was 20.4%, 23.0% and 13.0% in arms 1, 2 and 3, respectively. The 2 most common TEAEs leading to permanent discontinuation of study drug were renal impairment and neurotoxicity.

There were no clinically significant differences between treatment arms in the frequency of TEAEs of special interest. The proportion of patients who reported events of diabetes mellitus, neurological disorders, vascular disorders and cardiac disorders was similar between treatment arms. The proportion of patients who reported events of hypertension was 21.5%, 25.4% and 27.1% in arms 1, 2 and 3, respectively.

There were no clinically significant changes from baseline in vital sign results.

There were no clinically meaningful differences in safety results observed between treatment arms in male or female patients in this study. The proportion of male and female patients who reported TEAEs was similar between treatment arms (96.1%, 98.5% and 100% of male patients in arms 1, 2 and 3, respectively, and 98.8%, 98.8% and 97.6% of female patients in arms 1, 2 and 3, respectively). TEAEs reported by ≥ 20.0% of male patients in any treatment arm were anemia, diarrhea, hypertension, renal failure and pleural effusion. TEAEs reported by ≥ 20.0% of female patients in any treatment arm were diarrhea, anemia, hypertension, nausea, pleural effusion, leukopenia, liver transplant rejection, renal failure, hyperglycemia, cholestasis, vomiting and hyperkalemia.

There were no clinically meaningful differences in safety results observed between treatment arms within the age subgroups (< 50 years of age and ≥ 50 years of age) in this study. The proportion of patients < 50 and ≥ 50 years of age who reported TEAEs was similar between treatment arms (96.2%, 98.7% and 100% of patients < 50 years of age in arms 1, 2 and 3, respectively, and 97.1%, 98.6% and 99.0% of patients ≥ 50 years of age in arms 1, 2 and 3, respectively). TEAEs reported by ≥ 20.0% of patients < 50 years of age in any treatment arm were anemia, diarrhea, hypertension, hyperglycemia, liver transplant rejection, leukopenia, pleural effusion, renal failure, thrombocytopenia, nausea and pyrexia. TEAEs reported by ≥ 20.0% of patients ≥ 50 years of age in any treatment arm were diarrhea, anemia, hypertension, renal failure and pleural effusion.

There were no clinically meaningful differences in safety results observed between treatment arms within the donor type subgroups (living related, living nonrelated and deceased) in this study. Overall, 97.5% of patients received a liver from a deceased donor. TEAEs reported by patients who received a liver from a deceased donor were similar to those reported in the overall population as a whole. In patients who received a liver from a living related donor, the most common TEAE was liver transplant rejection. The 2 most common TEAEs in patients who received a liver from a living nonrelated donor were renal failure and pleural effusion.

CONCLUSIONS: Based on the efficacy results of this study in liver transplant recipients, arm 2 (slightly reduced initial Advagraf dose, with basiliximab) showed improvements in renal function, acute rejection rate and rate of BCAR compared with arms 1 and 3.

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

This study demonstrated that an immunosuppressive regimen of Advagraf (immediately or delayed posttransplant) and MMF with or without a monoclonal anti-IL2R antibody (basiliximab) and optional corticosteroid bolus is safe and efficacious in liver transplant recipients.

Date of Report: 06 February 2014

Table 1 Patient Disposition

Number (%) of Patients				
Prior to randomization	**Arm 1 (n = 309)**	**Arm 2 (n = 298)**	**Arm 3 (n = 294)**	**Total (n = 901)**
Screened†	309 (100)	298 (100)	294 (100)	901 (100)
Randomized in eCRF	304 (98.4)	298 (100)	291 (99.0)	893 (99.1)
Randomized in eCRF and transplanted (SAF)	295 (95.5)	286 (96.0)	276 (93.9)	857 (95.1)
After randomization	**Arm 1 (n = 298)**	**Arm 2 (n = 303)**	**Arm 3 (n = 292)**	**Total (n = 893)**
SAF‡	289 (97.0)	291 (96.0)	277 (94.9)	857 (96.0)
Modified ITT	289 (97.0)	291 (96.0)	277 (94.9)	857 (96.0)
FAS	283 (95.0)	287 (94.7)	274 (93.8)	844 (94.5)
PPS	214 (71.8)	215 (71.0)	214 (73.3)	643 (72.0)

All patients who were transplanted (SAF and Modified ITT); all enrolled patients who were transplanted and received at least one dose of study medication (Advagraf, basiliximab or MMF) (FAS); all patients from the FAS who did not have any PPS violations (PPS)

Patient No. [redacted] ([redacted], arm 1) was enrolled and dosed but not properly consented. Due to local patient data protection laws, data for Patient No. [redacted] was not allowed in the clinical database and was not included in the tables or listings.

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

eCRF: electronic case report form; FAS: Full Analysis Set; ITT: intent-to-treat; IVRS: Interactive Voice Response System; MMF: mycophenolate mofetil; PPS: Per Protocol Set; SAF: Safety Analysis Set

† All screened patients were randomized in IVRS, as the start of the study quickly followed screening. Some patients were not included in the eCRF (e.g., they did not consent to participate or did not meet inclusion/exclusion criteria).

‡ Six patients (Patient Nos. [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]) who were randomized to arm 1 received basiliximab perioperatively, so these patients were assigned to arm 2. For Patient No. [redacted] who was randomized to arm 2, Advagraf was delayed; this patient was assigned to arm 3.

Source: Tables 12.1.1.1 and 12.1.1.2

Table 2 Demographic and Baseline Characteristics (Safety Analysis Set)

Parameter Statistic	**Arm 1 (n = 289)**	**Arm 2 (n = 291)**	**Arm 3 (n = 277)**	**Total (n = 857)**
Sex, n (%)				
Male	205 (71.2)	206 (70.8)	193 (69.7)	604 (70.6)
Female	83 (28.8)	85 (29.2)	84 (30.3)	252 (29.4)
Not recorded	1	0	0	1
Race, n (%)				
White	277 (96.2)	271 (93.1)	259 (93.5)	807 (94.3)
Black/African	1 (0.3)	7 (2.4)	8 (2.9)	16 (1.9)
Asian	1 (0.3)	3 (1.0)	2 (0.7)	6 (0.7)
Other	9 (3.1)	10 (3.4)	8 (2.9)	27 (3.2)
Not recorded	1	0	0	1
Age group, n (%)				
< 50 years	78 (27.1)	79 (27.1)	74 (26.7)	231 (27.0)
50 to 65 years	189 (65.6)	188 (64.6)	175 (63.2)	552 (64.5)
66 to 75 years	21 (7.3)	24 (8.2)	28 (10.1)	73 (8.5)
Not recorded	1	0	0	1

Table continued on next page

Parameter Statistic	**Arm 1** **(n = 289)**	**Arm 2** **(n = 291)**	**Arm 3** **(n = 277)**	**Total** **(n = 857)**
Age, years				
n	288	291	277	856
Mean (SD)	54.4 (9.10)	53.8 (9.89)	53.7 (10.57)	54.0 (9.86)
Median	55	55	55	55
Minimum to maximum	26 - 73	19 - 73	19 - 75	19 - 75
Height, cm				
n	287	290	275	852
Mean (SD)	170.96 (8.999)	171.23 (9.434)	170.89 (9.843)	171.03 (9.416)
Median	171	172	171	171
Minimum to maximum	145 - 193	142 - 193	145 - 196	142 - 196
Weight, kg				
n	287	290	273	850
Mean (SD)	77.05 (16.452)	77.95 (17.022)	78.33 (16.319)	77.77 (16.596)
Median	75	76	77	76
Minimum to maximum	43 - 128	38 - 153	38 - 132	38 - 153
BMI, kg/m^2				
n	286	289	272	847
Mean (SD)	26.29 (4.845)	26.55 (5.449)	26.71 (4.801)	26.52 (5.043)
Median	25.80	25.70	26.35	26.00
Minimum to maximum	14.4 - 42.5	14.9 - 55.0	15.6 - 46.6	14.4 - 55.0
ABO blood type, n (%)				
A	130 (45.1)	136 (46.7)	127 (45.8)	393 (45.9)
AB	14 (4.9)	18 (6.2)	13 (4.7)	45 (5.3)
B	38 (13.2)	39 (13.4)	36 (13.0)	113 (13.2)
O	106 (36.8)	98 (33.7)	101 (36.5)	305 (35.6)
Not recorded	1	0	0	1
Viral status, n (%)				
HIV negative	283 (98.3)	289 (99.3)	270 (97.5)	842 (98.4)
HIV unknown	5 (1.7)	2 (0.7)	7 (2.5)	14 (1.6)
HBV negative	251 (87.2)	248 (85.2)	244 (88.1)	743 (86.8)
HBV positive	35 (12.2)	42 (14.4)	29 (10.5)	106 (12.4)
HBV unknown	2 (0.7)	1 (0.3)	4 (1.4)	7 (0.8)
HCV negative	195 (67.7)	209 (71.8)	197 (71.1)	601 (70.2)
HCV positive	90 (31.3)	80 (27.5)	79 (28.5)	249 (29.1)
HCV unknown	3 (1.0)	2 (0.7)	1 (0.4)	6 (0.7)
CMV negative	93 (32.3)	94 (32.3)	90 (32.5)	277 (32.4)
CMV positive	180 (62.5)	191 (65.6)	177 (63.9)	548 (64.0)
CMV unknown	15 (5.2)	6 (2.1)	10 (3.6)	31 (3.6)
EBV negative	26 (9.0)	32 (11.0)	27 (9.7)	85 (9.9)
EBV positive	232 (80.6)	221 (75.9)	214 (77.3)	667 (77.9)
EBV unknown	30 (10.4)	38 (13.1)	36 (13.0)	104 (12.1)
Not recorded	1	0	0	1

All patients who were transplanted (SAF)

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

BMI: body mass index; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MMF: mycophenolate mofetil; SAF: Safety Analysis Set

Source: Tables 12.1.2.1.1, 12.1.4.1.1 and 12.1.4.2.1

Table 3 Glomerular Filtration Rate (GFR) at 24 Weeks After Transplantation Estimated by MDRD4 Formula (mL/min/1.73 m^2)

Statistic	Arm 1	Arm 2	Arm 3	Arm 2 – Arm 1	Arm 3 – Arm 1	Arm 2 – Arm 3
Full Analysis Set (FAS) – planned treatment						
n	284	278	268	NA		
Unadjusted mean (SD)	59.9 (32.99)	69.9 (37.28)	66.0 (32.54)			
LS mean	66.8	77.0	73.0	10.2	6.2	4.0
P value†	NA			< 0.001	0.034	0.131
Two-sided CI†				(4.4, 16.0)	(0.4, 12.0)	(-1.2, 9.1)
Full Analysis Set (FAS) – actual treatment						
n	278	283	269	NA		
Unadjusted mean (SD)	60.4 (33.06)	69.1 (37.34)	66.1 (32.51)			
LS mean	67.4	76.4	73.3	9.1	5.9	3.1
P value†	NA			0.001	0.047	0.230
Two-sided CI†				(3.3, 14.8)	(0.1, 11.8)	(-2.0, 8.3)
Per Protocol Set (PPS)						
n	213	213	212	NA		
Unadjusted mean (SD)	62.7 (30.72)	67.7 (31.30)	67.4 (29.74)			
LS mean	74.7	79.3	79.2	4.6	4.5	0.1
P value†	NA			0.120	0.133	0.958
Two-sided CI†				(-1.0, 10.1)	(-1.1, 10.0)	(-4.8, 5.1)

Covariates – P values from F-tests			
Statistic	**FAS – Planned Treatment**	**FAS – Actual Treatment**	**PPS**
Pooled site	< 0.001	< 0.001	< 0.001
Sex	< 0.001	< 0.001	0.005
Race	0.018	0.017	< 0.001
HCV at baseline	0.359	0.354	0.258
Baseline GFR	< 0.001	< 0.001	< 0.001

All enrolled patients who were transplanted and received at least one dose of study medication (Advagraf, basiliximab or MMF) (FAS); all patients from the FAS who did not have any PPS violations (PPS)

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

ANCOVA: analysis of covariance; FAS: Full Analysis Set; GFR: glomerular filtration rate; HCV: hepatitis C virus; LS: least square; MDRD4: Modification Diet in Renal Disease 4; MMF: mycophenolate mofetil; NA: not applicable; PPS: Per Protocol Set

† For the comparisons of arm 1 to arm 2 and of arm 1 to arm 3 P values, standard errors and CIs were adjusted according to the Dunnett procedure. The P value and the standard error for the comparison of arm 2 to arm 3 were not adjusted. The CI for the comparison of arm 2 to arm 3 has a 95% level.

Source: Tables 12.3.1.1, 12.3.1.2 and 12.3.1.3

Table 4 Primary and Secondary Measures of Renal Function

GFR Measurement (mL/min/1.73 m^2)	Total Number of Patients	Arm 2 – Arm 1 LS Mean (95% CI)	Arm 2 – Arm 1 P value†	Arm 3 – Arm 1 LS Mean (95% CI)	Arm 3 – Arm 1 P value†	Arm 2 – Arm 3 LS Mean (95% CI)	Arm 2 – Arm 3 P value†	P value: Actual Treatment Group
Full Analysis Set								
MDRD4	830	9.1 (3.3, 14.8)	0.001	5.9 (0.1, 11.8)	0.047	3.1 (-2.0, 8.3)	0.230	0.002
CKD-EPI	830	7.8 (2.7, 12.9)	0.002	5.3 (0.1, 10.5)	0.046	2.5 (-2.1, 7.1)	0.282	0.003
Creatinine clearance	830	9.5 (3.6, 15.5)	< 0.001	5.7 (-0.4, 11.7)	0.071	3.9 (-1.4, 9.2)	0.152	0.002
Cystatin C	606	4.3 (-2.4, 11.1)	0.268	4.4 (-2.4, 11.2)	0.256	-0.1 (-6.2, 5.9)	0.972	0.254
Iohexol clearance	528	0.3 (-9.4, 10.1)	0.945	-3.9 (-13.8, 6.1)	0.445	4.2 (-5.6, 14.1)	0.401	0.652
Per Protocol Set								
MDRD4	638	4.6 (-1.0, 10.1)	0.120	4.5 (-1.1, 10.0)	0.133	0.1 (-4.8, 5.1)	0.958	0.113
CKD-EPI	638	5.1 (-0.2, 10.4)	0.063	3.9 (-1.3, 9.2)	0.173	1.1 (-3.6, 5.8)	0.636	0.084
Creatinine clearance	638	5.9 (0.0, 11.8)	0.049	4.7 (-1.2, 10.6)	0.139	1.2 (-4.0, 6.5)	0.642	0.064
Cystatin C	539	4.2 (-2.8, 11.3)	0.302	4.4 (-2.5, 11.4)	0.271	-0.2 (-6.4, 6.1)	0.952	0.279
Iohexol clearance	496	0.0 (-10.2, 10.2)	0.995	-7.0 (-17.3, 3.3)	0.182	7.0 (-3.3, 17.3)	0.180	0.305

All enrolled patients who were transplanted and received at least one dose of study medication (Advagraf, basiliximab or MMF) (FAS); all patients from the FAS who did not have any PPS violations (PPS)

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; FAS: Full Analysis Set; GFR: glomerular filtration rate; LS: least square; MDRD4: Modification Diet in Renal Disease formula 4; MMF: mycophenolate mofetil; PPS: Per Protocol Set

† P values, standard errors and 95% CIs were calculated without any adjustment for multiple testing.

Source: Tables 12.3.1.1, 12.3.1.2, 12.3.3.11.1, 12.3.3.11.2, 12.3.3.12.1, 12.3.3.12.2, 12.3.3.13.1, 12.3.3.13.2, 12.3.3.14.1 and 12.3.3.14.2

Table 5 TEAEs Reported by ≥ 10.0% of Patients in Any Treatment Arm (Safety Analysis Set)

MedDRA (v11.1) SOC Preferred Term, n (%)	Arm 1 (n = 289)	Arm 2 (n = 291)	Arm 3 (n = 277)	Total (n = 857)
Blood and lymphatic system disorders				
Anaemia	97 (33.6)	84 (28.9)	87 (31.4)	268 (31.3)
Leukopenia	50 (17.3)	49 (16.8)	52 (18.8)	151 (17.6)
Thrombocytopenia	50 (17.3)	50 (17.2)	44 (15.9)	144 (16.8)
Gastrointestinal disorders				
Diarrhoea	88 (30.5)	84 (28.9)	84 (30.3)	256 (29.9)
Nausea	60 (20.8)	42 (14.4)	47 (17.0)	149 (17.4)
Abdominal pain	33 (11.4)	38 (13.1)	34 (12.3)	105 (12.3)
Constipation	26 (9.0)	32 (11.0)	46 (16.6)	104 (12.1)
Vomiting	38 (13.1)	31 (10.7)	31 (11.2)	100 (11.7)
Vascular disorders				
Hypertension	62 (21.5)	74 (25.4)	74 (26.7)	210 (24.5)
Hypotension	30 (10.4)	34 (11.7)	26 (9.4)	90 (10.5)
Metabolism and nutrition disorders				
Hyperglycaemia	49 (17.0)	54 (18.6)	37 (13.4)	140 (16.3)
Hyperkalaemia	41 (14.2)	42 (14.4)	29 (10.5)	112 (13.1)
Hypokalaemia	24 (8.3)	30 (10.3)	25 (9.0)	79 (9.2)
Renal and urinary disorders				
Renal failure	75 (26.0)	61 (21.0)	55 (19.9)	191 (22.3)
Renal failure acute	29 (10.0)	26 (8.9)	23 (8.3)	78 (9.1)
General disorders and administration site conditions				
Pyrexia	44 (15.2)	35 (12.0)	45 (16.2)	124 (14.5)
Oedema peripheral	32 (11.1)	35 (12.0)	32 (11.6)	99 (11.6)
Respiratory, thoracic and mediastinal disorders				
Pleural effusion	75 (26.0)	55 (18.9)	54 (19.5)	184 (21.5)
Immune system disorders				
Liver transplant rejection	56 (19.4)	38 (13.1)	53 (19.1)	147 (17.2)
Hepatobiliary disorders				
Cholestasis	38 (13.1)	44 (15.1)	44 (15.9)	126 (14.7)
Psychiatric disorders				
Insomnia	28 (9.7)	36 (12.4)	35 (12.6)	99 (11.6)
Nervous system disorders				
Tremor	30 (10.4)	29 (10.0)	30 (10.8)	89 (10.4)
Musculoskeletal and connective tissue disorders				
Back pain	32 (11.1)	28 (9.6)	21 (7.6)	81 (9.5)

All patients who were transplanted (SAF)

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

MMF: mycophenolate mofetil; SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.17

Table 6 Serious TEAEs (Including Deaths) Reported by ≥ 2.0% of Patients in Any Treatment Arm (Safety Analysis Set)

MedDRA (v11.1) SOC Preferred Term, n (%)	**Arm 1 (n = 289)**	**Arm 2 (n = 291)**	**Arm 3 (n = 277)**	**Total (n = 857)**
Total patients with at least one serious TEAE	**189 (65.4)**	**174 (59.8)**	**177 (63.9)**	**540 (63.0)**
Infections and infestations				
Pneumonia	10 (3.5)	8 (2.7)	7 (2.5)	25 (2.9)
Sepsis	9 (3.1)	11 (3.8)	3 (1.1)	23 (2.7)
Cytomegalovirus infection	6 (2.1)	4 (1.4)	7 (2.5)	17 (2.0)
Septic shock	1 (0.3)	2 (0.7)	6 (2.2)	9 (1.1)
Injury, poisoning and procedural complications				
Complications of transplanted liver	6 (2.1)	6 (2.1)	10 (3.6)	22 (2.6)
Biliary anastomosis complication	9 (3.1)	3 (1.0)	6 (2.2)	18 (2.1)
Post procedural haemorrhage	4 (1.4)	8 (2.7)	4 (1.4)	16 (1.9)
Transplant failure	6 (2.1)	1 (0.3)	0	7 (0.8)
Renal and urinary disorders				
Renal failure	18 (6.2)	19 (6.5)	15 (5.4)	52 (6.1)
Renal failure acute	16 (5.5)	13 (4.5)	14 (5.1)	43 (5.0)
Gastrointestinal disorders				
Intra-abdominal haemorrhage	5 (1.7)	7 (2.4)	4 (1.4)	16 (1.9)
Ascites	6 (2.1)	2 (0.7)	6 (2.2)	14 (1.6)
Hepatobiliary disorders				
Bile duct stenosis	6 (2.1)	3 (1.0)	11 (4.0)	20 (2.3)
Respiratory, thoracic and mediastinal disorders				
Respiratory failure	13 (4.5)	11 (3.8)	4 (1.4)	28 (3.3)
Pleural effusion	8 (2.8)	6 (2.1)	9 (3.2)	23 (2.7)
Immune system disorders				
Liver transplant rejection	25 (8.7)	19 (6.5)	27 (9.7)	71 (8.3)
Nervous system disorders				
Neurotoxicity	6 (2.1)	4 (1.4)	0	10 (1.2)

All patients who were transplanted (SAF)

Arm 1: Advagraf + MMF + corticosteroids

Arm 2: Advagraf + MMF + basiliximab + corticosteroids

Arm 3: delayed Advagraf + MMF + basiliximab + corticosteroids

MMF: mycophenolate mofetil; SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.11