| | | |
|---|---|---|
| **Name of Sponsor/Company:** Astellas Pharma Global Development | | |
| **Name of Finished Product:** NA | | |
| **Name of Active Ingredient:** Tacrolimus Granules | | |

## SYNOPSIS

**Title of Study:** An Open, Randomised, Comparative, Multicentre Paediatric Clinical Trial Comparing the Efficacy and Safety of a Dual Regimen With Oral Tacrolimus (FK506) Versus a Triple Regimen With Oral Cyclosporin-Microemulsion in Primary Liver Allograft Transplantation

**Investigators/Coordinating Investigator:** [redacted]

**Study Center(s):** This multicenter study was conducted at 10 contracted sites in a total of 6 countries including Belgium (1 site), France (2 sites), Germany (3 sites), Italy (1 site), Spain (2 sites) and the UK (1 site).

**Publication Based on the Study:**

Kelly D, Jara P, Rodeck B, Lykavieris P, Burdelski M, Becker M, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. Lancet. 2004;364:1054-61.

Kelly D. Safety and efficacy of tacrolimus in pediatric liver recipients. Pediatr Transplant. 2011;15:19–24.

Reding R. Tacrolimus in pediatric liver transplantation. Pediatr Transplantation. 2002;6:447-51.

**Study Period:** 3.3 years

**Study Initiation Date (Date of First Enrollment):** 02 Jun 1997

**Study Completion Date (Date of Last Evaluation):** 23 Dec 2000

**Phase of Development:** Phase 3

**Objectives:** To investigate the safety and efficacy of a tacrolimus based regimen using a new formulation (fine granules) in comparison to a cyclosporin-microemulsion (ME) based standard regimen in children receiving a primary liver transplant.

**Methodology:** This was an open-label, randomized, multicenter, pediatric phase 3 study in primary liver allograft transplantation comparing a tacrolimus based dual drug immunosuppressive regimen (i.e., tacrolimus granules with low-dose corticosteroids) with a cyclosporin-ME based triple drug immunosuppressive regimen (i.e., cyclosporin-ME with low-dose corticosteroids and azathioprine).

Patients undergoing a primary liver allograft transplantation were enrolled into the study. Randomization was to be performed directly before the first administration of study drug, usually within 6 h posttransplantation. In case of postoperative renal impairment, the randomization could be delayed up to 24 h posttransplantation.

After the initial screening on day 0 (day of skin closure), patients were observed for efficacy and safety variables over a period of 12 months. Study visits were scheduled at days 1, 5, 9, 14, 21 and 30; weeks 6, 8, 10

and 12; and months 6, 9 and 12. Time windows of ± 2 and ± 7 days were acceptable for study visits 1 to 10 and study visits 11 to 13, respectively.

During the study, patients were observed for rejection episodes and adverse events (AEs). Changes in study drug dosing and concomitant medication (including immunosuppressive medication) were recorded at each visit and the whole blood trough levels of tacrolimus were measured. The microbiological status and incidence of posttransplant lymphoproliferative disease (PTLD) was also assessed.

**Number of Patients (Planned, Enrolled and Analyzed):** A total of 200 patients (100 patients per arm) were to be enrolled.

Of the patients who were transplanted, 91 patients received tacrolimus and 90 patients received cyclosporin-ME.

**Diagnosis and Main Criteria for Inclusion:** Patients were eligible to enter the study if they fulfilled the following criteria:

1. Pediatric patients undergoing primary liver allograft transplantation (cadaveric or living related donor).
2. Male or female patients ≤ 16 years of age with a maximum weight of 40 kg, regardless of race.
3. The patient's parent or legal representative had given written informed consent. In addition, if the patient was able to understand the concept of informed consent, the child's written informed consent had also been obtained.

**Test Product, Dose and Mode of Administration, Batch Numbers:** Patients were treated with tacrolimus granules, as part of a dual immunosuppressive treatment regimen.

The planned initial daily dose was 0.3 mg/kg per day orally, given in 2 doses (equals 0.15 mg/kg twice daily) postoperatively. Intravenous administration was only commenced when it was impossible or inappropriate to administer tacrolimus orally. The first dose of 0.15 mg/kg of tacrolimus was to be administered as soon as possible after surgery but no longer than 6 h (24 h in case of postoperative renal impairment) after closure of the skin. The recommended target whole blood trough levels of tacrolimus were 10 to 20 ng/mL during the first 2 weeks after transplantation, 10 to 15 ng/mL during weeks 3 and 4, 5 to 15 ng/mL during months 2 and 3 and 5 to 10 ng/mL thereafter. Dose adjustments were to be made on the basis of the patient's overall clinical status and trough concentrations. Of the tacrolimus granules, 6 batches of 0.2 mg and 8 batches of 1.0 mg were used. Of the injectable form of tacrolimus, 8 batches of 5 mg/mL ampoules were used.

Methylprednisolone (10 mg/kg) was administered intravenously during surgery. Postoperative corticosteroid treatment consisted of intravenous methylprednisolone on days 1 to 6 (2 mg/kg per day) and once daily oral prednisolone thereafter. The dose of prednisolone was 1 mg/kg on days 7 to 13, 0.75 mg/kg on days 14 to 20, 0.5 mg/kg on days 21 to 28 and 0.25 mg/kg at months 2 to 3. Thereafter, prednisolone was to be taken every other day and/or tapered off, according to local practice.

**Duration of Treatment (or Duration of Study, if applicable):** 12 months

**Reference Product, Dose and Mode of Administration, Batch Numbers:** Cyclosporin-ME, as part of a triple immunosuppressive treatment regimen.

The planned initial daily dose for cyclosporin-ME was 10 mg/kg per day orally, given in 2 doses (equals 5 mg/kg twice daily). The first dose of 5 mg/kg of cyclosporin-ME was to be administered as soon as possible

after surgery but no longer than 6 h (24 h in case of postoperative renal impairment) after closure of the skin. The recommended target whole blood trough levels of cyclosporin were 250 to 350 ng/mL within the first 2 weeks after transplantation, 200 to 300 ng/mL during weeks 3 to 12, 150 to 200 ng/mL during months 4 to 12 and 100 to 150 ng/mL thereafter. Dose adjustments were to be made on the basis of the patient's overall clinical status and trough concentrations. Two batches of Neoral (100 mg/mL) were used.

Corticosteroid doses were the same as for the tacrolimus immunosuppressive treatment regimen (see above).

Azathioprine was to be administered at a dose of 1.5 mg/kg per day during the first 3 months, after which it was to be administered according to local practice.

**Criteria for Evaluation:** The primary efficacy endpoint was the incidence and time to first acute rejection.

The secondary efficacy variables were

- Incidence and time to steroid-resistant acute rejection
- Patient and graft survival (graft loss was defined as retransplantation or death, whichever occurred earlier)
- Cumulative concomitant immunosuppressive medication over time (the analyses of this data are presented along with the data of other concomitant medications)

The safety variables were overall incidence of AEs and the incidence of diabetes mellitus, hypertension and lymphoproliferative disease.

**Statistical Methods:**

*Population for Analysis:* The intent-to-treat (ITT) population consisted of all randomized patients with results attributed to the treatment group that they were randomized to and who received at least 1 dose of study drug.

The efficacy population consisted of all randomized patients with results attributed to the treatment group that they were randomized to and who received at least 1 dose of study drug. Patients who had displayed major protocol violations were excluded from the efficacy population. There were no major protocol violations; therefore, the efficacy population was not implemented.

*Efficacy:* The efficacy parameters to be analyzed were the incidence and time to onset of acute rejection, the incidence and time to onset of steroid-resistant acute rejection, patient and graft survival rates and the cumulative concomitant immunosuppressive medication over time. Regarding the latter efficacy parameter, however, only use of immunosuppressive medication for maintenance therapy (i.e., corticosteroid by patients in the tacrolimus granules group and corticosteroid and azathioprine by patients in the cyclosporin-ME group) was summarized over time for this report and this analysis was presented in the section on study drug exposure.

The time to first acute rejection was to be analyzed using Kaplan-Meier survival procedures. Treatment comparisons were to be based on the Wilcoxon test on a 5% level of significance. Patients that discontinued study drug were to be censored at the day of the 12-month follow-up visit whereas others (completers) were to be censored at the day of the month 12 visit. Biopsy-proven acute rejections and steroid-resistant acute rejections were to be analyzed similarly.

Patient and graft survival were also to be analyzed using Kaplan-Meier survival procedures with treatments compared using the Wilcoxon test. Patients that discontinued study drug were to be censored on the day of the day of the month 12 visit.

For all efficacy and safety endpoints, age < 5 years and ≥ 5 years were used for subgroup analysis of age rather than age < 3 years and ≥ 3 years. The analyses with age cutoff of 5 years were conducted to comply with a US regulatory requirement. The results of these analyses are considered descriptive. Subgroup analyses for living versus cadaveric donors were not performed.

At the time this study was conducted, an exploratory Cox's proportional hazards analysis was planned to be done on acute rejection, steroid resistant acute rejection AR, steroid resistant AR, graft survival and patient survival to assess the effect that center, age group, sex, cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), primary diagnosis have on outcome. However, because both tacrolimus and the effects of various factors on acute rejection and survival are now relatively well understood, this analysis was no longer deemed necessary and therefore not performed.

*Safety:* AEs were summarized using the sponsor-modified Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) coding system suitable for transplantation. All AEs starting on or after the day of skin closure were included in analyses of AEs. AEs were not summarized over time nor were they compared between treatment groups using statistical tests.

Overall incidence of infections was to be summarized for the categories 'Bacterial,' 'Viral,' 'Fungal,' 'Protozoal' and 'Other' or 'Not Confirmed.'

A planned summary of the following AEs of special interest was outlined in the clinical trial analysis plan (CTAP): neurological events, nephrological disorders and glucose disorders. A list of COSTART terms included in the CTAP for the first 2 of these groups was to be used to group these events. However, it was determined later that the lists in the CTAP were incomplete; therefore, the analyses in this report use all terms appropriate to the groups.

In addition to the groups of special interest listed above, cardiac events were also to be summarized as a group of special interest; this report, however, summarizes cardiovascular events instead, as cardiovascular events include all cardiac terms (except cardiomegaly and pericardial effusion) as well as other events of interest (e.g., hypertension). This report also summarizes malignancy and PTLD as groups of special interest. Due to the low number of events, PTLD was not summarized over time as planned in the CTAP; due to the complicated nature of diagnosing this event of special interest, it was instead summarized as either suspected or established PTLD.

Laboratory data summaries were to be included. The mean and SD for each laboratory parameter, at screening, days 1, 5, 9, 14 and 21, weeks 6 and 10 and months 1, 2, 3, 6, 9 and 12 were to be presented. Laboratory data were converted to values in SI-units, if recorded in any other unit. Prothrombin time was listed but not summarized. Similarly, ethylenediaminetetraacetic acid clearance, which was sparsely collected, was listed but not summarized; however, estimated glomerular filtration rate was calculated using the age-appropriate Schwartz formula and summarized over time.

The mean, SD, minimum and maximum for each vital sign, at screening, days 1, 5, 9, 14 and 21, weeks 6 and 10 and months 1, 2, 3, 6, 9 and 12 were to be presented. Growth performance was assessed via height and weight as presented in the summary of vital signs.

Microbiology and echocardiography results at screening were listed only and not analyzed by visit. Reasons for hospitalization and intensive care unit were also listed but not summarized.

**Summary of Results/Conclusions:**

**Patient Disposition:** Of the patients who were transplanted, 91 patients received tacrolimus and 90 patients received cyclosporin-ME [Figure 1]. These patients were included in the ITT population. One additional patient was randomized to tacrolimus granules but received cyclosporin-ME and discontinued study drug after the first dose. This patient was excluded from the ITT analysis as no further data were collected; at the patient's 12-month follow up visit, it was confirmed that the patient was still alive and the patient's transplant was functioning.

**Demographics:**

*Recipients*

Demographic characteristics were generally comparable between the tacrolimus granules and the cyclosporin-ME groups [Table 1]. In both the tacrolimus granules and cyclosporin-ME groups, approximately half of patients were male (50.5% and 53.5%, respectively), the majority of patients was Caucasian (82.4% and 88.9%, respectively). The mean age was 3.54 years in the tacrolimus granules group and 3.47 years in the cyclosporin-ME group. The mean weight was 14.58 kg in the tacrolimus granules group and 13.86 kg in the cyclosporin-ME group.

In both the tacrolimus granules and cyclosporin-ME groups, the majority of patients were < 5 years of age (76.9% and 77.8%, respectively) [Table 1]. The proportion of patients < 1 year of age was 34.1% in the tacrolimus granules group and 42.2% in the cyclosporin-ME group.

*Donors*

In both the tacrolimus granules and the cyclosporin-ME groups, the majority of donors was male (62.9% and 56.8%, respectively) and Caucasian (84.9% and 85.9%, respectively) [Table 1]. The mean age was 16.86 years in the tacrolimus granules group and 17.76 years in the cyclosporin-ME group.

**Efficacy Results:**

Over the 12-month study in children receiving a primary liver transplant, the Kaplan Meier estimate for the rate of first acute rejection, shown in [Figure 2], and first steroid-resistant acute rejection were significantly lower in the tacrolimus granules group than in the cyclosporin-ME group ($P = 0.030$ and $P < 0.001$, respectively; Wilcoxon test). The corresponding rates at 12 months were also significantly lower in the tacrolimus granules group compared to the cyclosporin-ME group (first acute rejection: 44.5% and 59.8%, respectively; first steroid-resistant acute rejection: 4.6% and 28.6%, respectively).

Among patients ≥ 5 years of age and < 1 year of age, no statistical significance was reached for the Kaplan-Meier estimate for the rate of first acute rejection over the 12-month study or for the corresponding rate at 12 months. Among patients < 5 years of age, the Kaplan Meier estimate for the rate of first acute rejection over the 12-month study was significantly lower in the tacrolimus granules group ($P = 0.015$, Wilcoxon test), but the corresponding rate at 12 months was not statistically significant.

The interaction between treatment and sex with regard to acute rejection was driven largely by the disparity between acute rejection rates in female patients, which were approximately 2-fold higher in female patients in the cyclosporin-ME group than in female patients in the tacrolimus granules group.

At 12 months, the tacrolimus granules and cyclosporin-ME groups had comparable rates for patient survival (93.4% and 92.2%, respectively) and graft survival (92.3% and 85.4%, respectively).

**Safety Results:**

Over the 12-month study in children receiving a primary liver transplant, the incidence of AEs and AEs assessed by the investigator as related to study drug was comparable between the tacrolimus granules and cyclosporin-ME groups (94.5% and 90.0%, respectively) Table 2. For the most common (≥ 20% of patients in either treatment group) AEs, treatment differences were noted for Epstein-Barr virus (EBV) infection (26.4% and 11.1%, respectively) and hirsutism (1.1% and 27.8%, respectively). Most of the events of EBV infection (25.3% and 10.0%, respectively) and hirsutism (0 and 26.7%, respectively) were assessed by the investigator as related to study drug.

Five patients (2 tacrolimus granules, 3 cyclosporin-ME) died while on study drug and 11 patients (5 tacrolimus granules, 6 cyclosporin-ME) died after they discontinued study drug.

In the tacrolimus granules and cyclosporin-ME groups, at least 1 SAE was reported for 83.5% and 76.7% of patients, respectively Table 3. The most common (≥ 10% of patients in either treatment group) SAEs were fever, liver function tests abnormal, CMV infection and diarrhea.

The proportion of patients experiencing AEs leading to discontinuation of study drug (i.e., change in study drug was “discontinued” on the AE case report form) was comparable between the tacrolimus granules and cyclosporin-ME groups (12.1% and 14.4%, respectively).

The incidence of AEs of special interest (i.e., infections, nephrological disorders, glucose metabolism disorders, neurological disorders and cardiovascular events) was comparable between the tacrolimus granules and cyclosporin-ME groups. Most infections in the tacrolimus granules group were not identified: 61.5% compared to 38.9% in the cyclosporin-ME group. The tacrolimus granules and cyclosporin-ME groups had a low and comparable incidence of hyperglycemia (5.5% and 3.3%, respectively) and diabetes mellitus (2.2% and 2.2%, respectively). The incidence in the tacrolimus granules and cyclosporin-ME groups was low for the AEs of special interest of malignancy events (5 patients and none), suspected PTLD (2 patients and 1 patient) and established PTLD (3 patients and none in the cyclosporin-ME group). The difference in incidence of suspected and established PTLD was not unexpected.

No medically unexpected events were observed with tacrolimus granules regardless of age or sex. The treatment differences noted in the incidence of common (≥ 10% in either treatment group) AEs and the incidence of the most common (≥ 10% in either treatment group) SAEs are consistent with the known safety profiles of tacrolimus and cyclosporin.

There were no unexpected clinically relevant changes in laboratory evaluations or vital signs results.

**CONCLUSIONS:**

Tacrolimus granules as part of a dual drug immunosuppressive regimen were efficacious when compared to a cyclosporin-ME based triple drug immunosuppressive regimen in lowering acute rejection rates over 12 months after pediatric primary liver allograft transplantation.

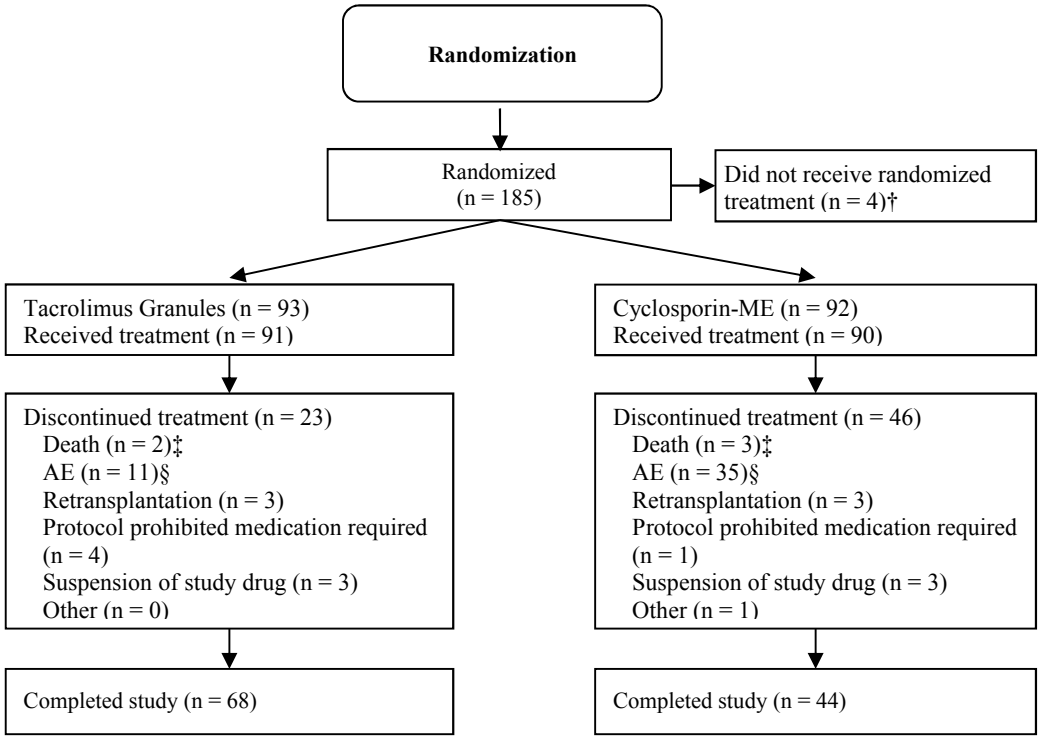
Steroid-resistant acute rejection rates were also lower over 12 months after tacrolimus granules compared to cyclosporin-ME. Rates for patient survival and graft survival were comparable between the 2 treatment groups.

The efficacy results were similar regardless of age.

Although the safety profile slightly differed, both treatments can be considered well tolerated.

**Date of Report:** 25 Apr 2017

**Figure 1 Disposition of Patients**




AE: adverse event; CRF: case report form; ME: microemulsion

† Three patients (1 randomized to tacrolimus granules and 2 randomized to cyclosporin-ME) did not receive treatment. One additional patient was randomized to tacrolimus granules but received cyclosporin-ME and discontinued after the first dose. No further data were collected for this patient.

‡ An additional 11 patients (5 tacrolimus granules, 6 cyclosporin-ME) died after they discontinued from the study.

§ Reason for discontinuation on the Study Completion CRF was "AE."

Source: Tables 12.1.1.2, 12.1.1.3.1, 12.1.1.4.1 and Appendix 13.2.1.1

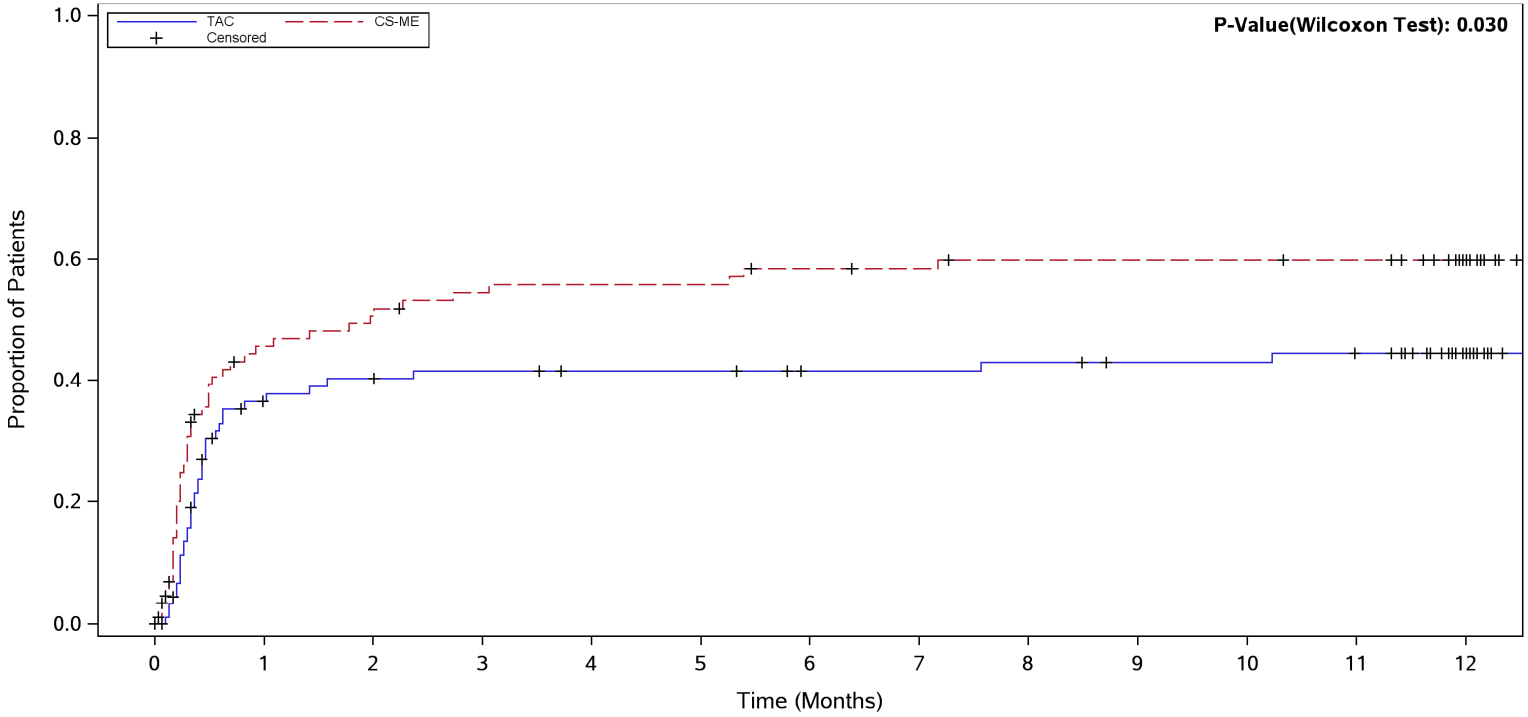
**Table 1 Summary of Demographics and Baseline Characteristics in Recipients and Donors (ITT Population)**

| Parameter Category/Statistics | Tacrolimus Granules n = 91 | Cyclosporin-ME n = 90 |
|---|---|---|
| Sex, n (%) (Recipient) | | |
| Male | 46 (50.5) | 48 (53.3) |
| Female | 45 (49.5) | 42 (46.7) |
| Sex, n (%) (Donor) | | |
| Male | 56 (62.9) | 50 (56.8) |
| Female | 33 (37.1) | 38 (43.2) |
| Missing | 2 | 2 |
| Race, n (%) (Recipient) | | |
| Black | 6 (6.6) | 2 (2.2) |
| Caucasian | 75 (82.4) | 80 (88.9) |
| Oriental | 5 (5.5) | 3 (3.3) |
| Other | 4 (4.4) | 5 (5.6) |
| Unknown | 1 (1.1) | 0 |
| Race, n (%) (Donor) | | |
| Black | 1 (1.2) | 0 |
| Caucasian | 73 (84.9) | 73 (85.9) |
| Unknown | 12 (14.0) | 12 (14.1) |
| Missing | 5 | 5 |
| Recipient age, years | | |
| n | 91 | 90 |
| Mean (SD) | 3.544 (3.942) | 3.466 (4.213) |
| Age subgroup, n (%) (Recipient) | | |
| < 5 years | 70 (76.9) | 70 (77.8) |
| ≥ 5 years | 21 (23.1) | 20 (22.2) |
| < 1 year | 31 (34.1) | 38 (42.2) |
| ≥ 1 year | 60 (65.9) | 52 (57.8) |
| Donor age, years | | |
| n | 89 | 89 |
| Mean (SD) | 16.86 (14.80) | 17.76 (13.23) |
| Recipient weight, kg | | |
| n | 91 | 89 |
| Mean (SD) | 14.58 (10.30) | 13.86 (10.74) |
| Recipient height, cm | | |
| n | 77 | 69 |
| Mean (SD) | 88.7 (28.3) | 87.7 (26.9) |

ITT: intent-to-treat; ME: microemulsion.

Source: Tables 12.1.2.1.1 and 12.1.2.4.1

**Figure 2 Kaplan-Meier Plot of Time to First Acute Rejection (ITT Population)**




Number of Subjects At Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TAC | 91 | 52 | 48 | 46 | 44 | 44 | 41 | 41 | 40 | 38 | 38 | 36 | 20 |
| CS-ME | 90 | 43 | 39 | 35 | 34 | 34 | 31 | 30 | 28 | 28 | 28 | 27 | 17 |

CS-ME: cyclosporin-microemulsion; ITT: intent-to-treat; TAC: tacrolimus

Source: Figure 12.3.1

**Table 2 Summary of Common (≥ 10% in Either Treatment Group) AEs (COSTART) (ITT Population)**

| COSTART System Organ Class<br>Preferred Term | Number of Patients, n (%)<br>Tacrolimus Granules n = 91 | <br>Cyclosporin-ME n = 90 |
|---|---|---|
| **Any AE** | **89 (97.8)** | **88 (97.8)** |
| **Body as a Whole** | **78 (85.7)** | **77 (85.6)** |
| Fever | 42 (46.2) | 46 (51.1) |
| Infection | 23 (25.3) | 26 (28.9) |
| Sepsis | 20 (22.0) | 18 (20.0) |
| CMV infection | 14 (15.4) | 22 (24.4) |
| EBV infection | 24 (26.4) | 10 (11.1) |
| Ascites | 15 (16.5) | 18 (20.0) |
| Peritonitis | 11 (12.1) | 6 (6.7) |
| **Cardiovascular System** | **50 (54.9)** | **53 (58.9)** |
| Hypertension | 35 (38.5) | 42 (46.7) |
| **Digestive System** | **73 (80.2)** | **63 (70.0)** |
| Liver function tests abnormal | 34 (37.4) | 25 (27.8) |
| Diarrhea | 24 (26.4) | 23 (25.6) |
| Vomiting | 14 (15.4) | 12 (13.3) |
| Gastrointestinal hemorrhage | 10 (11.0) | 11 (12.2) |
| Bile duct disorder | 11 (12.1) | 7 (7.8) |
| Gastroenteritis | 11 (12.1) | 4 (4.4) |
| **Hemic and Lymphatic System** | **45 (49.5)** | **31 (34.4)** |
| Anemia | 26 (28.6) | 17 (18.9) |
| **Metabolic and Nutritional Disorders** | **55 (60.4)** | **44 (48.9)** |
| Hypomagnesemia | 36 (39.6) | 26 (28.9) |
| Acidosis | 24 (26.4) | 15 (16.7) |
| Hyperkalemia | 11 (12.1) | 9 (10.0) |
| **Respiratory System** | **46 (50.5)** | **37 (41.1)** |
| Pleural effusion | 20 (22.0) | 17 (18.9) |
| Bronchitis | 10 (11.0) | 7 (7.8) |
| **Skin and Appendages** | **16 (17.6)** | **30 (33.3)** |
| Hirsutism | 1 (1.1) | 25 (27.8) |
| **Urogenital System** | **27 (29.7)** | **22 (24.4)** |
| Kidney function abnormal | 12 (13.2) | 13 (14.4) |

AE: adverse event; CMV: cytomegalovirus; COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms; EBV: Epstein-Barr virus; ITT: intent-to-treat; ME: microemulsion.

Source: Table 12.6.1.2.1

**Table 3 Summary of Common (≥ 5% in Either Treatment Group) SAEs (COSTART) (ITT Population)**

| COSTART System Organ Class<br>Preferred Term | Number of Patients, n (%) | |
|---|---|---|
| | Tacrolimus Granules<br>n = 91 | Cyclosporin-ME<br>n = 90 |
| **Any SAE** | **76 (83.5)** | **69 (76.7)** |
| **Body as a Whole** | **40 (44.0)** | **48 (53.3)** |
| Fever | 20 (22.0) | 21 (23.3) |
| Sepsis | 9 (9.9) | 8 (8.9) |
| CMV infection | 4 (4.4) | 11 (12.2) |
| Ascites | 6 (6.6) | 8 (8.9) |
| Infection | 5 (5.5) | 4 (4.4) |
| EBV infection | 6 (6.6) | 2 (2.2) |
| **Cardiovascular System** | **17 (18.7)** | **17 (18.9)** |
| Hypertension | 5 (5.5) | 3 (3.3) |
| **Digestive System** | **50 (54.9)** | **41 (45.6)** |
| Liver function tests abnormal | 17 (18.7) | 15 (16.7) |
| Bile duct disorder | 8 (8.8) | 7 (7.8) |
| Diarrhea | 6 (6.6) | 9 (10.0) |
| Gastrointestinal hemorrhage | 7 (7.7) | 8 (8.9) |
| Vomiting | 4 (4.4) | 7 (7.8) |
| Gastroenteritis | 8 (8.8) | 2 (2.2) |
| **Nervous System** | **8 (8.8)** | **6 (6.7)** |
| Convulsion | 5 (5.5) | 2 (2.2) |
| **Respiratory System** | **15 (16.5)** | **11 (12.2)** |
| Pleural effusion | 5 (5.5) | 5 (5.6) |
| **Urogenital System** | **10 (11.0)** | **7 (7.8)** |
| Kidney function abnormal | 5 (5.5) | 5 (5.6) |

CMV: cytomegalovirus; COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms; EBV: Epstein-Barr virus; ITT: intent-to-treat; ME: microemulsion; SAE: serious adverse event.

Source: Table 12.6.1.7.1