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

SYNOPSIS

Title of Study: A Multicentre, Open-label, Pharmacokinetic Study of Modigraf® (Tacrolimus Granules) in *de Novo* Paediatric Allograft Recipients

Investigators/Coordinating Investigator: [redacted]

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

Publication Based on the Study: Not applicable

Study Period: 3.7 years

Study Initiation Date (Date of First Enrollment): 09 Jun 2011

Study Completion Date (Date of Last Evaluation): 03 Feb 2015

Phase of Development: Phase 4

Objectives:

- To determine the pharmacokinetics of tacrolimus following oral administration of Modigraf, after the first oral dose and at steady state in pediatric patients undergoing de novo allograft transplantation.
- To determine safety and efficacy of Modigraf.

Methodology: This was a multicenter, open-label, single arm study. Pediatric patients undergoing liver, kidney or heart transplantation and meeting the inclusion criteria and complying with the exclusion criteria prior to initiation of tacrolimus therapy were enrolled.

Prior to enrollment, informed consent (IC) was obtained from the patient's parent(s) or their legal representative(s). Assent from the patient was also obtained where applicable.

Patients were treated with a tacrolimus-granule (Modigraf)-based immunosuppressive regimen.

The initial daily dose for Modigraf was 0.3 mg/kg per day orally given in 2 doses (equals 0.15 mg/kg twice daily) postoperatively. The first dose of 0.15 mg/kg of tacrolimus was to be administered within 24 h after reperfusion (this period may have been extended up to 5 days for heart transplant recipients).

Subsequent oral tacrolimus doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and observing the following recommended whole blood trough level range of 5 to 20 ng/mL.

Two pharmacokinetic profiles were taken as follows:

Profile 1: First dose of tacrolimus after reperfusion

Profile 2: Day 7 (+ 7 days) after a minimum of 4 days without a dose change (due to the higher clearance in very young children this may have been possible after 3 days).

Study patients were closely followed through the reporting of serious adverse events (SAEs). SAEs were reported to regulatory bodies by Astellas, as appropriate. No additional safety committees were used and an interim analysis was not planned.

On completion of the end of study visit (ESV) for Study F506-CL-0403, patients may have been enrolled into the follow-up Study F506-CL-0404, a long-term, open-label, noncomparative study to evaluate the safety and efficacy of a Modigraf based immunosuppression regimen in pediatric solid allograft recipients.

Number of Patients (Planned, Enrolled and Analyzed): Assuming a drop-out rate of 40%, approximately 60 patients were to be enrolled into the study in order to achieve 36 evaluable patients, 12 (± 2) of each indication liver, kidney and heart transplant, with 2 complete evaluable pharmacokinetic profiles.

Out of 53 screened patients, 52 patients were transplanted and received treatment (17 patients with heart transplant, 20 patients with liver transplant and 15 patients with kidney transplant). There was 1 screening failure.

Diagnosis and Main Criteria for Inclusion: A patient was eligible for the study if all of the following applied:

1. The patient was 12 years of age or younger.
2. The patient was the recipient of a solid organ (liver, kidney or heart) transplant. Multiorgan transplants were acceptable as long as one of the organs transplanted was liver, kidney or heart.
3. The patient's parent(s) or their legal representative(s) had been fully informed and had given written IC to participate in the study. The patient had given assent where applicable.

Test Product, Dose and Mode of Administration, Batch Numbers: Patients were treated with a Modigraf (tacrolimus granules) based immunosuppressive regimen. The initial daily dose for Modigraf was 0.3 mg/kg per day orally, given in 2 doses (equals 0.15 mg/kg twice daily) postoperatively. The first dose of 0.15 mg/kg of tacrolimus was to be administered in the morning within 24 h after reperfusion (this period may have been extended up to 5 days for heart transplant recipients). Three batches each of 0.2 and 1.0 mg were used.

Duration of Treatment (or Duration of Study, if applicable): This was a 2-week treatment study.

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

Criteria for Evaluation: The efficacy of Modigraf was described from the following parameters:

- Rejection episodes:
  - Acute rejection episodes;
  - Biopsy-proven acute rejection (BPAR) episodes;
  - Severity of BPAR.
- Patient and graft survival:
  - Death and reason for death;
  - Graft loss and reason for graft loss.

The following pharmacokinetic parameters for tacrolimus were determined after the morning dose on day 1 and day 7: AUC_{tau}, C_{max}, t_{max} and C_{trough}. Dose was optimized by monitoring tacrolimus whole blood trough levels, using local assay, for example by immunoassay or liquid chromatography-tandem mass spectrometry in the local laboratories.

The safety and tolerability of the test drug were assessed using AEs, vital signs and clinical laboratory.

Statistical Methods: All analyses were performed by type of organ transplant (liver, kidney and heart transplant) and overall. All data processing, summarization, and analyses were performed using statistical analysis software (SAS)® Version 9.1.3 or higher on Unix.

Population for Analysis: The safety analysis set (SAF) consisted of all patients who took at least 1 dose of study medication.

The extended pharmacokinetic set (EPKS) included all patients from the SAF population for whom sufficient plasma concentration data was available to facilitate derivation of at least 1 primary pharmacokinetic parameter.

The pharmacokinetic analysis set (PKAS) included all patients from EPKS who provided 2 complete pharmacokinetic profiles (on day 1, after the first dose of tacrolimus after transplantation and at day 7).

Efficacy: Summaries of acute rejection as well as BPAR episodes according to "Banff 97 07 update" (for patients with kidney transplant), "Histological Grading of Liver Biopsies for Rejection" and the "Standardized nomenclature of the international Society of Heart and Lung Transplantation" were presented. Severity of BPAR was tabulated.

Incidence rate of acute rejection, BPAR and patient death were described at each visit, for each of the 3 types of organ transplant and overall.

Patient survival was summarized descriptively. Graft loss was only listed. Additionally the findings from each biopsy and the reasons for patient death were listed.

Analyses were performed for the SAF.

Pharmacokinetics: Whole blood concentration data were used to obtain the following pharmacokinetic parameters: $AUC_{tau,}$ t_{max}, C_{max}, and $C_{trough.}$ AUC_{0-12} was calculated using the trapezoidal rule.

All pharmacokinetic data was listed and summarized in tabular or graphical form, as appropriate.

The correlation between C_{trough} and AUC_{tau} was assessed by Pearson's coefficient at each sample time by visit. Data were presented graphically.

Analyses were performed for the EPKS and PKAS.

Safety: AEs were collected and coded with MedDRA v15.0. Incidence of treatment-emergent AEs (TEAEs), treatment-emergent SAEs, TEAEs causally related to study drug (considered by the investigator to be possibly or probably related to study drug or if relationship is missing) and TEAEs leading to discontinuation were summarized.

Results of laboratory parameters and vital signs (heart rate, systolic and diastolic blood pressure) were shown in a descriptive manner by visit. Additionally, changes from baseline were also summarized.

These analyses were presented for the SAF.

Summary of Results/Conclusions:

Subject Disposition: Out of 53 screened patients, 52 patients were transplanted and received treatment (17 patients with heart transplant, 20 patients with liver transplant and 15 patients with kidney transplant). There was 1 screening failure due to the administration of a prohibited medication [Figure 1].

All patients who took at least 1 dose of treatment were included in the SAF.

Overall, 38 (73.1%) patients were included in the PKAS (12 [70.6%] patients in the heart transplant group, 14 [70.0%] patients in the liver transplant group and 12 [80.0%] patients in the kidney transplant group).

Demographics:

Recipients

Overall, the majority of patients in the SAF were male (67.3%), white (94.2%) and under 5 years of age (69.2%). The mean age was 4.3 years. The mean weight was 15.15 kg [Table 1].

Donors

Overall, 53.8% of donors in the SAF were male (47.1% in the heart transplant group, 45.0% in the liver transplant group and 73.3% in the kidney transplant group). The mean age was 18.6 years (7.0 years in the heart transplant group, 37.0 years in the liver transplant group and 20.3 years in the kidney transplant group) [Table 1].

Efficacy and Pharmacokinetic Results:

Efficacy: Five patients experienced acute rejection episodes. In the heart transplant group, 2 patients had rejections with 1 classified as a BPAR. In the liver transplant group, 3 patients had rejections and all were classified as BPAR. No rejection occurred in the kidney transplant group [Table 2].

There were no deaths or graft losses.

Pharmacokinetic: Out of 52 patients enrolled, 38 patients had 2 evaluable pharmacokinetic profiles. Overall, the mean AUC_{tau} for the first pharmacokinetic profile (day 1) was 224.13 h*ng/mL in patients with heart transplant, 210.56 h*ng/mL in patients with liver transplant and 97.40 h*ng/mL in patients with kidney transplant. The mean AUC_{tau} for the second PK profile (week 1) was 165.17 h*ng/mL in patients with heart transplant, 195.08 h*ng/mL in patients with liver transplant and 208.32 h*ng/mL in patients with kidney transplant [Table 3 and Table 4].

Overall, C_{trough} and AUC_{tau} were positively correlated both at day 1 and week 1 on the PKAS (Pearson's coefficients were 0.81 and 0.87, respectively).

Safety Results: Overall, 46 (88.5%) patients reported at least 1 TEAE. The most frequently reported common (≥ 10% in any organ transplant) TEAEs were hypertension (13 [25.0%] patients) followed by diarrhea (9 [17.3%] patients) and vomiting (8 [15.4%] patients) [Table 5].

Overall, 34 (65.4%) patients reported at least 1 drug-related TEAE. The most commonly reported drug-related TEAEs were hypertension (10 [19.2%] patients) followed by toxicity to various agents (6 [11.5%] patients).

Overall, 17 (32.7%) patients reported at least 1 serious TEAE. The most commonly reported serious TEAEs were toxicity to various agents and blood creatinine increased (3 [5.8%] patients each) [Table 6].

One patient with liver transplant reported 2 TEAEs (vomiting and toxicity to various agents, reported term "toxic tacrolimus level") resulting in treatment discontinuation.

The incidence of TEAEs was similar in patients under 5 years of age and in patients 5 years of age or older (32 [88.9%] and 14 [87.5%], respectively). No unexpected clinically relevant differences between both age categories were identified.

Overall, there were no unexpected clinically relevant changes in laboratory evaluations or vital signs results.

There were no deaths.

CONCLUSIONS:

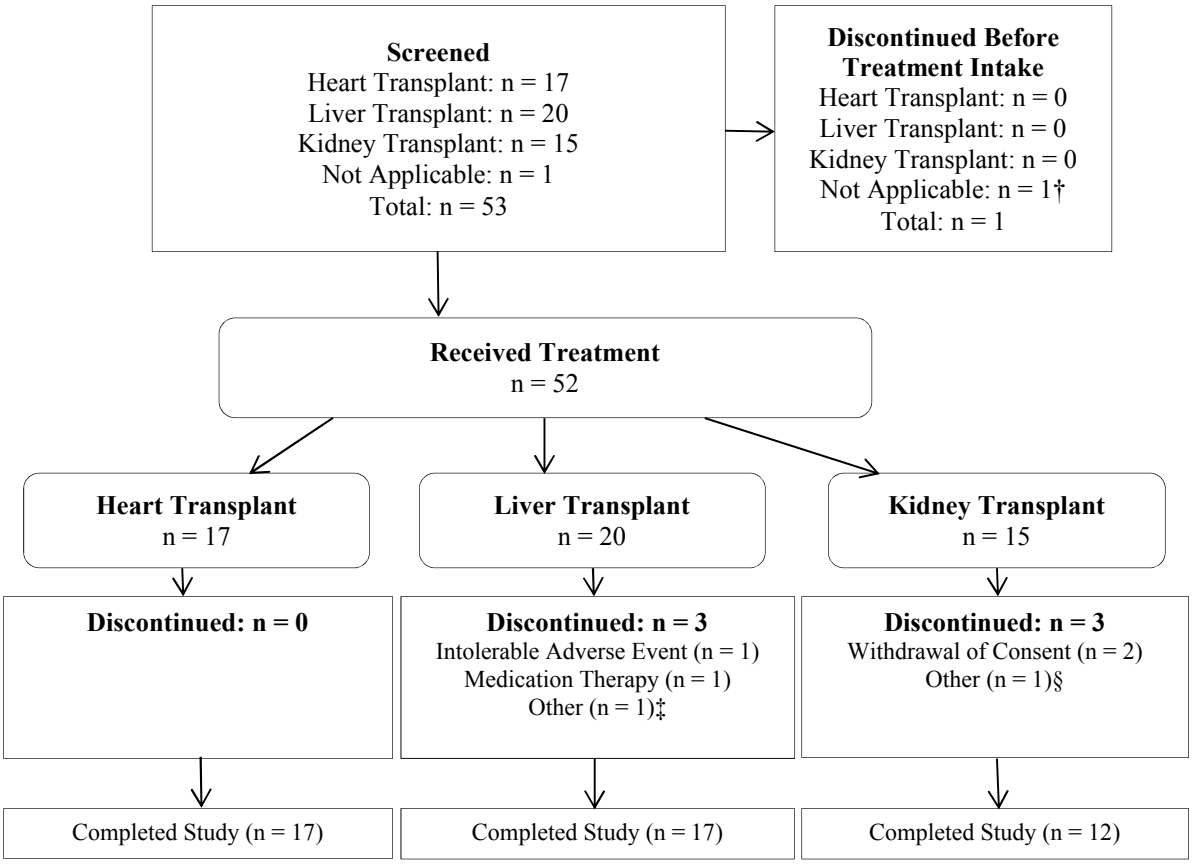
Thirty-eight (38) of the 52 treated pediatric patients had 2 evaluable pharmacokinetic profiles. There was strong correlation between C_{trough} and AUC_{tau}.

Few rejections were observed which is consistent with the short-term period of the study. No graft loss and no deaths occurred.

In this study, tacrolimus granules (Modigraf) were safe and well-tolerated when used in de novo pediatric allograft recipients for up to 2 weeks. The numbers of TEAEs and SAEs were not unexpected in this transplanted population in the immediate postoperative period. The safety profile is in keeping with the known characteristics of tacrolimus, and no new safety issues were identified.

Date of Report: 25 May 2016

Figure 1 Disposition of Patients



† Screen failure patient is counted as "Not Applicable" since no organ transplant data have been collected.

‡ Taken prohibited medication in the trial.

§ Pharmacokinetic profile 1 not completed.

Source: Tables 12.1.1.1, 12.1.1.3.1, 12.1.1.4 and Appendix 13.2.1.2

Table 1 Summary of Demographics and Baseline Characteristics in Recipients and Donors (SAF)

Parameter Category/ Statistics	Heart Transplant (n = 17)	Liver Transplant (n = 20)	Kidney Transplant (n = 15)	Total (n = 52)
Sex, n (%) (Recipient)				
Male	13 (76.5%)	10 (50.0%)	12 (80.0%)	35 (67.3%)
Female	4 (23.5%)	10 (50.0%)	3 (20.0%)	17 (32.7%)
Sex, n (%) (Donor)				
Male	8 (47.1%)	9(45.0%)	11 (73.3%)	28 (53.8%)
Female	8 (47.1%)	11 (55.0%)	4 (26.7%)	23 (44.2%)
Missing	1 (5.9%)	0	0	1 (1.9%)
Race, n (%) (Recipient)				
White	17 (100.0%)	18 (90.0%)	14 (93.3%)	49 (94.2%)
Black or African American	0	0	0	0
Asian	0	0	1 (6.7%)	1 (1.9%)
Other	0	2 (10.0%)	0	2 (3.8%)
Recipient Age (Years)				
n	17	20	15	52
Mean (SD)	5.2 (4.2)	2.6 (3.2)	5.4 (3.0)	4.3 (3.7)
Recipient Age subgroup (Years)				
< 5 years	9 (52.9%)	17 (85.0%)	10 (66.7%)	36 (69.2%)
≥ 5 years	8 (47.1%)	3 (15.0%)	5 (33.3%)	16 (30.8%)
Recipient Age subgroup 2				
0 ≤ days≤ 27 days(Newborn)	0	0	0	0
≥ 28 days to ≤ 23 months (Infants and Toddlers)	5 (29.4%)	12 (60.0%)	0	17(32.7%)
≥ 2 years to ≤ 11 years (Children)	11 (64.7%)	8 (40.0%)	15 (100.0%)	34 (65.4%)
≥ 12 years to ≤ 17 years (Adolescents)	1 (5.9%)	0	0	1 (1.9%)
Donor Age (Years)				
n	10	6	3	19
Mean (SD)	7.0 (4.5)	37.0 (10.1)	20.3 (20.3)	18.6 (16.5)
Recipient Weight (kg)				
n	16	20	15	51
Mean (SD)	17.18 (8.96)	12.35 (8.41)	16.74 (5.30)	15.15 (8.00)
Recipient Height (cm)				
n	16	19	14	49
Mean (SD)	104.00 (26.33)	84.12 (22.74)	100.33 (13.97)	95.24 (23.36)

SAF: safety analysis set.

Source: Table 12.1.2.1.1

Table 2 Number of Patients with Acute Rejections and BPARs by Transplanted Organ (SAF)

Parameters	Heart Transplant (n = 17)	Liver Transplant (n = 20)	Kidney Transplant (n = 15)
All Rejections	**2 (11.8%)**	**3 (15.0%)**	**0**
BPARs	1 (5.9%)	3 (15.0%)	0
NonBPARs	1 (5.9%)	0	0
Any Acute Rejection	**2 (11.8%)**	**3 (15.0%)**	**0**
Spontaneously resolving Acute Rejections†	1 (5.9%)	1 (5.0%)	0
Corticosteroid Sensitive Acute Rejections‡	1 (5.9%)	2 (10.0%)	0
Corticosteroid Resistant Acute Rejections§	0	0	0
BPAR	**1 (5.9%)**	**3 (15.0%)**	**0**
Spontaneously Resolving Acute Rejections†	1 (5.9%)	1 (5.0%)	0
Corticosteroid Sensitive Acute Rejections‡	0	2 (10.0%)	0
Corticosteroid Resistant Acute Rejections§	0	0	0

BPAR: biopsy-proven acute rejection; SAF: safety analysis set.

Footnotes continued on next page

† A spontaneously resolving rejection is defined as a rejection episode which has not been treated with any new or increased corticosteroid medication, antibodies or any other medication and which has resolved, irrespective of any Modigraf® dose changes.

‡ A corticosteroid sensitive acute rejection is defined as a rejection episode treated with new or increased corticosteroid medication only and which has resolved, irrespective of any Modigraf® dose changes.

§ A corticosteroid resistant acute rejection is defined as a rejection episode which did not resolve following treatment with corticosteroids. If a rejection episode was not treated with corticosteroids first, but only with antibodies, it was nevertheless be included into this category.

Source: Table 12.3.1.1

Table 3 Summary of Whole Blood Pharmacokinetic Parameters (Day 1) (PKAS)

Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
Heart Transplant				
Overall				
n	12	12	12	12
Mean (SD)	224.13 (114.30)	45.61 (19.55)	2.953 (4.328)	12.60 (13.40)
Median	198.03	47.50	1.000	7.93
Min – Max	66.6 - 475.6	15.0 - 71.2	0.50 - 12.00	2.4 - 49.6
GM	199.00	41.20	1.300	8.80
< 5 Years				
n	5	5	5	5
Mean (SD)	169.67 (106.70)	36.50 (21.48)	1.300 (1.525)	6.46 (4.04)
Median	139.55	28.10	0.500	4.77
Min – Max	66.6 - 348.3	15.0 - 69.5	0.50 - 4.00	2.4 - 12.5
GM	147.00	31.80	0.900	5.50
≥ 5 Years				
n	7	7	7	7
Mean (SD)	263.04 (110.10)	52.11 (16.56)	4.133 (5.375)	16.98 (16.26)
Median	237.86	49.60	1.000	9.85
Min – Max	152.5 - 475.6	27.6 - 71.2	0.50 - 12.00	5.7 - 49.6
GM	246.00	49.60	1.800	12.30
Liver Transplant				
Overall				
n	14	14	14	14
Mean (SD)	210.56 (84.01)	25.11 (10.78)	2.727 (1.837)	13.41 (7.11)
Median	206.61	23.10	2.017	10.55
Min – Max	108.0 - 411.8	11.8 - 47.5	0.98 - 8.10	5.0 - 25.5
GM	196.00	23.20	2.300	11.80
< 5 Years				
n	12	12	12	12
Mean (SD)	200.34 (86.56)	24.97 (11.70)	2.174 (0.938)	11.52 (5.70)
Median	191.83	22.05	2.000	10.20
Min – Max	108.0 - 411.8	11.8 - 47.5	0.98 - 4.00	5.0 - 25.5
GM	186.00	22.70	2.000	10.40
≥ 5 Years				
n	2	2	2	2
Mean (SD)	271.89 (23.93)	26.00 (1.98)	6.050 (2.899)	24.75 (0.35)
Median	271.89	26.00	6.050	24.75
Min – Max	255.0 - 288.8	24.6 - 27.4	4.00 - 8.10	24.5 - 25.0
GM	271.00	26.00	5.700	24.70
Kidney Transplant				
Overall				
n	12	12	12	12
Mean (SD)	97.40 (36.77)	18.04 (8.10)	1.776 (0.880)	3.54 (1.45)
Median	99.15	18.75	1.992	3.41
Min – Max	38.1 - 146.8	6.9 - 30.1	0.97 - 4.03	1.6 - 6.2

Table continued on next page

Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
GM	90.00	16.10	1.600	3.30
< 5 Years				
n	8	8	8	8
Mean (SD)	104.13 (39.63)	19.44 (7.69)	1.527 (0.576)	3.59 (1.55)
Median	108.37	19.70	1.500	3.23
Min – Max	38.1 - 146.8	7.3 - 30.1	0.97 - 2.20	2.0 - 6.2
GM	95.90	17.80	1.400	3.30
≥ 5 Years				
n	4	4	4	4
Mean (SD)	83.92 (30.51)	15.22 (9.31)	2.275 (1.252)	3.44 (1.44)
Median	89.33	13.40	2.000	3.60
Min – Max	47.1 - 109.9	6.9 - 27.2	1.07 - 4.03	1.6 - 5.0
GM	79.30	13.10	2.000	3.20
Total				
Overall				
n	38	38	38	38
Mean (SD)	179.11 (99.81)	29.35 (17.55)	2.498 (2.691)	10.04 (9.59)
Median	144.76	24.55	2.000	6.30
Min – Max	38.1 - 475.6	6.9 - 71.2	0.50 - 12.00	1.6 - 49.6
GM	154.00	24.80	1.700	7.20
< 5 Years				
n	25	25	25	25
Mean (SD)	163.42 (87.47)	25.51 (13.95)	1.792 (1.017)	7.97 (5.61)
Median	139.55	22.80	2.000	6.19
Min – Max	38.1 - 411.8	7.3 - 69.5	0.50 - 4.00	2.0 - 25.5
GM	143.00	22.50	1.500	6.40
≥ 5 Years				
n	13	13	13	13
Mean (SD)	209.29 (117.98)	36.75 (21.69)	3.856 (4.149)	14.01 (13.94)
Median	199.21	27.60	2.000	7.37
Min – Max	47.1 - 475.6	6.9 - 71.2	0.50 - 12.00	1.6 - 49.6
GM	176.00	29.80	2.300	9.00

GM: geometric mean; PKAS: pharmacokinetic analysis set.

C_{trough} is the trough whole blood concentration (measured at the end of a dosing interval at steady state directly before next administration).

For 1 patient, AUC was extrapolated to 12 h as t_{last} = 11.38 h for the day 1 pharmacokinetic profile. For another patient, AUC was interpolated to 12 h as t_{last} = 12.5 h for the day 1 pharmacokinetic profile.

Source: Table 12.4.2.2

Table 4 Summary of Whole Blood Pharmacokinetic Parameters (Week 1) (PKAS)

Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
Heart Transplant				
Overall				
n	12	12	12	12
Mean (SD)	165.17 (39.12)	32.69 (9.78)	0.838 (0.438)	7.57 (1.80)
Median	147.07	31.95	0.775	7.43
Min – Max	131.8 - 259.9	19.2 - 50.3	0.50 - 2.00	4.6 - 10.9
GM	161.00	31.40	0.800	7.40
< 5 Years				
n	5	5	5	5
Mean (SD)	152.11 (29.45)	33.24 (11.29)	0.900 (0.652)	5.90 (0.80)
Median	140.55	38.60	0.500	6.06
Min – Max	134.7 - 204.2	19.2 - 46.0	0.50 - 2.00	4.6 - 6.8
GM	150.00	31.60	0.800	5.90
≥ 5 Years				
n	7	7	7	7
Mean (SD)	174.50 (44.54)	32.30 (9.50)	0.793 (0.250)	8.75 (1.25)
Median	170.65	30.30	0.967	8.76
Min – Max	131.8 - 259.9	23.2 - 50.3	0.50 - 1.00	6.8 - 10.9
GM	170.00	31.20	0.800	8.70
Liver Transplant				
Overall				
n	14	14	14	14
Mean (SD)	195.08 (94.63)	30.52 (19.35)	1.714 (1.117)	9.71 (4.03)
Median	184.77	23.15	1.500	9.63
Min – Max	80.5 - 438.8	9.0 - 83.0	0.50 - 4.00	4.5 - 18.5
GM	176.00	25.90	1.400	8.90
< 5 Years				
n	12	12	12	12
Mean (SD)	196.79 (102.72)	32.60 (20.24)	1.667 (1.207)	9.11 (4.05)
Median	174.65	28.85	1.000	8.43
Min – Max	80.5 - 438.8	9.0 - 83.0	0.50 - 4.00	4.5 - 18.5
GM	175.00	27.50	1.300	8.40
≥ 5 Years				
n	2	2	2	2
Mean (SD)	184.77 (9.38)	18.10 (0.85)	2.000 (0.000)	13.25 (1.48)
Median	184.77	18.10	2.000	13.25
Min – Max	178.1 - 191.4	17.5 - 18.7	2.00 - 2.00	12.2 - 14.3
GM	185.00	18.10	2.000	13.20
Kidney Transplant				
Overall				
n	12	12	12	12
Mean (SD)	208.32 (68.75)	36.63 (13.97)	1.093 (0.608)	8.92 (3.59)
Median	186.55	32.85	1.000	8.16
Min – Max	116.5 - 329.8	17.7 - 59.4	0.48 - 2.08	4.2 - 16.9
GM	198.00	34.20	0.900	8.30
< 5 Years				
n	8	8	8	8
Mean (SD)	187.19 (56.89)	34.25 (14.76)	0.935 (0.494)	7.69 (2.32)
Median	169.26	28.65	0.867	7.08
Min – Max	116.5 – 259.3	17.7 - 59.4	0.48 - 1.95	4.2 - 10.8
GM	180.00	31.60	0.800	7.40
≥ 5 Years				
n	4	4	4	4
Mean (SD)	250.58 (78.78)	41.38 (12.73)	1.408 (0.766)	11.38 (4.76)
Median	251.82	38.15	1.525	11.23
Min – Max	168.9 - 329.8	30.4 - 58.8	0.50 - 2.08	6.2 - 16.9

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Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
GM	241.00	40.00	1.200	10.60
Total				
Overall				
n	38	38	38	38
Mean (SD)	189.81 (72.97)	33.14 (14.99)	1.241 (0.866)	8.78 (3.36)
Median	172.59	31.25	1.000	8.43
Min – Max	80.5 - 438.8	9.0 - 83.0	0.48 - 4.00	4.2 - 18.5
GM	178.00	30.00	1.000	8.20
< 5 Years				
n	25	25	25	25
Mean (SD)	184.78 (78.87)	33.25 (16.53)	1.279 (0.977)	8.02 (3.28)
Median	156.08	32.10	1.000	6.79
Min – Max	80.5 - 438.8	9.0 - 83.0	0.48 - 4.00	4.2 - 18.5
GM	171.00	29.50	1.000	7.50
≥ 5 Years				
n	13	13	13	13
Mean (SD)	199.49 (61.82)	32.91 (12.10)	1.168 (0.628)	10.25 (3.14)
Median	183.07	30.40	1.000	8.96
Min – Max	131.8 - 329.8	17.5 - 58.8	0.50 - 2.08	6.2 - 16.9
GM	192.00	31.00	1.000	9.80

GM: geometric mean; PKAS: pharmacokinetic analysis set.

C_{trough} is the trough whole blood concentration (measured at the end of a dosing interval at steady state directly before next administration).

For 1 patient, AUC was extrapolated to 12 h as t_{last} = 11.38 for the day 1 pharmacokinetic profile. For another patient, AUC was interpolated to 12 h as t_{last} = 12.5 h for the day 1 pharmacokinetic profile.

Source: Table 12.4.2.2

Table 5 Summary of Common (≥ 10% in any Organ Transplant) TEAEs (MedDRA v15.0) (SAF)

MedDRA v15.0 System Organ Class Preferred Term	Number of Patients, n (%) Treatment Heart Transplant n = 17	Liver Transplant n = 20	Kidney Transplant n = 15	Total n = 52
Any AE	**13 (76.5%)**	**20 (100.0%)**	**11 (73.3%)**	**44 (84.6%)**
Gastrointestinal Disorders	**2 (11.8%)**	**12 (60.0%)**	**8 (53.3%)**	**22 (42.3%)**
Abdominal Distension	0	0	3 (20.0%)	3 (5.8%)
Ascites	0	4 (20.0%)	0	4 (7.7%)
Diarrhoea	2 (11.8%)	2 (10.0%)	5 (33.3%)	9 (17.3%)
Gastrointestinal Haemorrhage	0	3 (15.0%)	0	3 (5.8%)
Upper Gastrointestinal Haemorrhage	0	2 (10.0%)	0	2 (3.8%)
Vomiting	0	3 (15.0%)	5 (33.3%)	8 (15.4%)
Metabolism and Nutrition Disorders	**8 (47.1%)**	**8 (40.0%)**	**3 (20.0%)**	**19 (36.5%)**
Hyperglycaemia	1 (5.9%)	4 (20.0%)	0	5 (9.6%)
Hypokalaemia	3 (17.6%)	2 (10.0%)	1 (6.7%)	6 (11.5%)
Hypomagnesaemia	2 (11.8%)	1 (5.0%)	2 (13.3%)	5 (9.6%)
Hyponatraemia	3 (17.6%)	0	0	3 (5.8%)
Hypophosphataemia	0	0	2 (13.3%)	2 (3.8%)
Metabolic Acidosis	0	6 (30.0%)	0	6 (11.5%)
Vascular Disorders	**2 (11.8%)**	**10 (50.0%)**	**2 (13.3%)**	**14 (26.9%)**
Hypertension	2 (11.8%)	9 (45.0%)	2 (13.3%)	13 (25.0%)
Hypotension	0	2 (10.0%)	0	2 (3.8%)
Injury, Poisoning and Procedural Complications	**0**	**12 (60.0%)**	**1 (6.7%)**	**13 (25.0%)**
Abdominal Wound Dehiscence	0	3 (15.0%)	0	3 (5.8%)
Complications of Transplanted Liver	0	3 (15.0%)	0	3 (5.8%)
Post Procedural Bile Leak	0	4 (20.0%)	0	4 (7.7%)
Toxicity to Various Agents	0	5 (25.0%)	1 (6.7%)	6 (11.5%)
General Disorders and Administration Site Conditions	**0**	**9 (45.0%)**	**3 (20.0%)**	**12 (23.1%)**
Drug Withdrawal Syndrome	0	4 (20.0%)	0	4 (7.7%)
Irritability	0	2 (10.0%)	0	2 (3.8%)
Pyrexia	0	3 (15.0%)	3 (20.0%)	6 (11.5%)
Renal and Urinary Disorders	**4 (23.5%)**	**6 (30.0%)**	**0**	**10 (19.2%)**
Oliguria	0	2 (10.0%)	0	2 (3.8%)
Renal Failure	0	2 (10.0%)	0	2 (3.8%)
Renal Impairment	2 (11.8%)	2 (10.0%)	0	4 (7.7%)
Renal Injury	2 (11.8%)	0	0	2 (3.8%)
Respiratory, Thoracic and Mediastinal Disorders	**3 (17.6%)**	**7 (35.0%)**	**0**	**10 (19.2%)**
Atelectasis	1 (5.9%)	2 (10.0%)	0	3 (5.8%)
Bronchospasm	0	3 (15.0%)	0	3 (5.8%)
Diaphragmatic Paralysis	2 (11.8%)	0	0	2 (3.8%)
Pleural Effusion	1 (5.9%)	3 (15.0%)	0	4 (7.7%)
Investigations	**1 (5.9%)**	**2 (10.0%)**	**5 (33.3%)**	**8 (15.4%)**
Blood Creatinine Increased	1 (5.9%)	0	4 (26.7%)	5 (9.6%)
Gamma-glutamyltransferase Increased	0	2 (10.0%)	0	2 (3.8%)
Urine Output Decreased	0	0	2 (13.3%)	2 (3.8%)
Blood and Lymphatic System Disorders	**2 (11.8%)**	**2 (10.0%)**	**2 (13.3%)**	**6 (11.5%)**
Anaemia	2 (11.8%)	2 (10.0%)	2 (13.3%)	6 (11.5%)
Infections and Infestations	**0**	**6 (30.0%)**	**0**	**6 (11.5%)**
Abdominal Infection	0	2 (10.0%)	0	2 (3.8%)
Lower Respiratory Tract Infection Bacterial	0	2 (10.0%)	0	2 (3.8%)
Sepsis	0	2 (10.0%)	0	2 (3.8%)
Nervous System Disorders	**0**	**2 (10.0%)**	**1 (6.7%)**	**3 (5.8%)**
Tremor	0	2 (10.0%)	1 (6.7%)	3 (5.8%)

SAF: safety analysis set; TEAE: treatment-emergent adverse event. Source: Table 12.6.1.13

Table 6 Incidence of Serious TEAEs (SAF)

MedDRA v15.0 System Organ Class Preferred Term	Number of Patients, n (%) Treatment Heart Transplant n = 17	E	Liver Transplant n = 20	E	Kidney Transplant n = 15	E	Total n = 52	E
Any AE	**4 (23.5%)**	**4**	**9 (45.0%)**	**11**	**4 (26.7%)**	**4**	**17 (32.7%)**	**19**
Injury, Poisoning and Procedural Complications	**0**	**0**	**4 (20.0%)**	**4**	**0**	**0**	**4 (7.7%)**	**4**
Post Procedural Bile Leak	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Toxicity to Various Agents	0	0	3 (15.0%)	3	0	0	3 (5.8%)	3
Hepatobiliary Disorders	**0**	**0**	**3 (15.0%)**	**3**	**0**	**0**	**3 (5.8%)**	**3**
Hepatic Artery Occlusion	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Hepatic Artery Thrombosis	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Portal Vein Thrombosis	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Investigations	**0**	**0**	**0**	**0**	**3 (20.0%)**	**3**	**3 (5.8%)**	**3**
Blood Creatinine Increased	0	0	0	0	3 (20.0%)	3	3 (5.8%)	3
Gastrointestinal Disorders	**0**	**0**	**2 (10.0%)**	**2**	**0**	**0**	**2 (3.8%)**	**2**
Intra-abdominal Haemorrahage	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Mechanical Ileus	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Infections and Infestations	**0**	**0**	**1 (5.0%)**	**1**	**1 (6.7%)**	**1**	**2 (3.8%)**	**2**
Pneumonia	0	0	0	0	1 (6.7%)	1	1 (1.9%)	1
Sepsis	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Renal and Urinary Disorders	**1 (5.9%)**	**1**	**1 (5.0%)**	**1**	**0**	**0**	**2 (3.8%)**	**2**
Renal Failure	0	0	1 (5.0%)	1	0	0	1 (1.9%)	1
Renal Impairment	1 (5.9%)	1	0	0	0	0	1 (1.9%)	1
Respiratory, Thoracic and Mediastinal Disorders	**2 (11.8%)**	**2**	**0**	**0**	**0**	**0**	**2 (3.8%)**	**2**
Diaphragmatic Paralysis	1 (5.9%)	1	0	0	0	0	1 (1.9%)	1
Pneumothorax	1 (5.9%)	1	0	0	0	0	1 (1.9%)	1
Vascular Disorders	**1 (5.9%)**	**1**	**0**	**0**	**0**	**0**	**1 (1.9%)**	**1**
Aortic Stenosis	1 (5.9%)	1	0	0	0	0	1 (1.9%)	1

E: number of events; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.6.1