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

SYNOPSIS

Title of Study: A Long-term, Open-label, Non-comparative Study to Evaluate the Safety and Efficacy of a Modigraf® Based Immunosuppression Regimen in Paediatric Solid Allograft Recipients

Investigators/Coordinating Investigator: [redacted]

Study Center(s): This multicenter study was conducted at 11 contracted sites in a total of 6 countries including UK (2 sites), 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: 3.9 years

Study Initiation Date (Date of First Enrollment): 24 Jun 2011

Study Completion Date (Date of Last Evaluation): 06 May 2015

Phase of Development: 4

Objective: The objective of the study was to monitor the safety and efficacy of Modigraf (tacrolimus granules) in stable pediatric allograft recipients.

Methodology:

This was a multicentre, open-label, single arm study. Pediatric patients who had undergone liver, kidney or heart transplantation and met the inclusion criteria and complying with the exclusion criteria prior to initiation of tacrolimus therapy were enrolled. All patients had previously participated in Study F506-CL-0403. This extension study is divided into 2 parts, referred to as Study F506-CL-0404A and Study F506-CL-0404B. Study F506-CL-0404A aimed to provide safety and efficacy data whereas Study F506-CL-0404B aimed to generate data with regard to dose changes and tacrolimus whole blood trough levels after eventual conversion from Modigraf to Prograf. This synopsis presents the results from Study F506-CL-0404A. The results from Study F506-CL-0404B will be presented in a separate report.

Prior to enrolment, informed consent was obtained from the patient's legal representative. Assent from the patient was obtained where applicable.

Patients were treated with a Modigraf-based immunosuppressive regimen.

Patients began the study on the same dose regimen as they received at the end of the F506-CL-0403 study. Subsequent Modigraf doses might have been adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs) and taking into consideration the recommended whole blood trough level range of 5 to

20 ng/ml. Day 1 of this study was to follow the end of study visit of Study F506-CL-0403, however for logistical reasons it could have been on the same day.

Patients were enrolled in the study for a maximum period of 1 year or until commercial availability of Modigraf in the patient's country (whichever occurred first). If, however, commercial availability occurred before the 3-month visit, patients were to continue in the study and complete their end of study visit (Part A) (ESVA) at that visit. This ensured a minimum of 3 months safety and efficacy data per patient. If there was no commercial availability of Modigraf in the patient's country after 1 year, Astellas was to continue to provide Modigraf outside of the study until commercial availability or until the patient was converted to a twice-a-day commercial Prograf regimen. Patient visits took place at months 1, 2 and 3 and every 3 months thereafter until the ESVA after 12 months (latest possible time, minimum after 3 months). Following the ESVA, patients were converted to commercial Modigraf. Patients who were prematurely discontinued were also to complete an ESVA. If the investigator decided that a patient was immediately to be converted to Prograf, then the patient might have skipped the visits during the first year and was to proceed directly to Study F506-CL-0404B. In this case, an ESVA was to be performed before enrolment into Study F506-CL-0404B.

Number of Patients (Planned, Enrolled and Analyzed): No sample size calculations were performed. However, as this study was a follow up of the pharmacokinetic Study F506-CL-0403, the sample size was based on the number considered to be appropriate to define pharmacokinetics in this population. Approximately 40 to 60 patients were expected to be enrolled into the study.

Out of 52 patients who were transplanted and received treatment in Study F506-CL-0403, 47 were enrolled (33 children < 5 years and 14 children ≥ 5 years with informed consent) in this extension study F506-CL-0404A and no patient was discontinued before the treatment intake.

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

1. Patient was ≤ 12 years of age at enrolment into Study F506-CL-0403.
2. Patient received at least 1 dose of Modigraf in the F506-CL-0403 study.
3. In the opinion of the patient's investigating physician, the patient was to benefit from further treatment with Modigraf.
4. The patient's parent(s) or their legal representative(s) had been fully informed and had given written informed consent 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 white tacrolimus granules for oral suspension were available in sachets containing either 0.2 mg or 1 mg tacrolimus granules per sachet. The first dose of Modigraf for each individual patient was identical to the final dose at the end of Study F506-CL-0403 for respective patient. The first dose of Modigraf was to be administered on the morning of day 1. Subsequent oral tacrolimus doses were adjusted by the investigator based on clinical evidence of efficacy and occurrence of AEs and observing the recommended whole blood trough level range of 5 to 20 ng/ml. Ten batches each of 0.2 and 1.0 mg were used.

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

- Minimum time on study drug: 3 months.
- Maximum time on study drug: 1 year.

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

Criteria for Evaluation:

Efficacy:

The efficacy of Modigraf was described from the following parameters:

- Rejection episodes:
  - Acute rejection episodes: A biopsy was to be performed after the onset of clinical/laboratory signs indicative of possible rejection;
  - Biopsy-proven acute rejection (BPAR) episodes;
  - Severity of BPAR.
- Patient and graft survival:
  - Death and reason for death;
  - Graft loss.

Possible biopsy findings confirming an acute rejection are reported in the biopsy log below. The histological evaluation of the biopsy was performed following the "Histological Grading of Liver Biopsies for Rejection", the "Banff 97 diagnostic categories for renal allograft biopsies - Banff '07 update" or the "standardised nomenclature of the International Society of Heart and Lung Transplantation".

Biopsy Log

Organ	Possible Findings in Biopsy Log Confirming Acute Rejection
Heart	Grade 1R (mild), Grade 2R (moderate) or Grade 3R (severe)
Liver	Rejection Activity Index ≥ 3
Kidney	Acute antibody-mediated rejection I, II, and II, Acute T cell mediated rejection IA, IB, IIA, IIB and III

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

Statistical Methods: Analyses were performed separately in Part A by type of organ transplant (liver, kidney and heart transplant). All analyses were presented for the overall population and also by age group at the time of transplantation (age group < 5 years and ≥ 5 years).

All data processing, summarization and analyses were performed using SAS® Version 9.1.3 or higher on Unix.

Population for Analysis: All patients enrolled in part A who took at least 1 dose of Modigraf study drug were included in the safety analysis set (SAF). The SAF was used for analysis of part A data.

Efficacy: Acute rejection and BPAR were classified and their incidence was tabulated. BPAR was also summarized by severity. Patient deaths and relevant reasons were tabulated. Graft losses were tabulated. Graft losses were listed separately and were also included in AEs listings.

Safety: The coding dictionary for this study used to summarize AEs by SOC and preferred term was MedDRA v15.0. Incidence of treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious TEAEs, TEAEs leading to permanent discontinuation of study drug, common TEAEs (≥ 10 %) were summarized. By-patient listings were presented for AEs, drug-related AEs, serious adverse events (SAEs) and AE leading to permanent discontinuation of study drug.

Quantitative clinical laboratory variables, i.e., hematology and biochemistry, were summarized using descriptive statistics at each analysis visit. The number and percentage of patients below and above potentially clinically significant (PCS) pediatric cuts (PCS low, not PCS, PCS high) were summarized at each analysis visit.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature and weight) were summarized using descriptive statistics by analysis visit.

Summary of Results/Conclusions:

Patient Disposition: Out of 52 patients who were transplanted and received treatment in Study F506-CL-0403, 47 were enrolled (33 children < 5 years and 14 children ≥ 5 years with informed consent) in this extension Study F506-CL-0404A and no patient was discontinued before the treatment intake. Out of the 5 patients who were not enrolled in this extension study, 3 patients with kidney transplant discontinued Study F506-CL-0403 and 2 patients with liver transplant completed Study F506-CL-0403 [Figure 1].

All 47 enrolled patients took at least 1 dose of Modigraf study drug and were included in the SAF.

Demographics:

Recipients

Overall, the majority of patients in the SAF were male (68.1%), white (97.9%) and < 5 years (70.2%). The mean age at enrollment was 4.2 years. The mean weight was 14.54 kg [Table 1].

Donors

Overall, 51.1% of donors in the SAF were male (47.1% in the heart transplant group, 44.4% in the liver transplant group and 66.7% in the kidney transplant group). The mean age was 7.0 years in the heart transplant group, 39.8 years in the liver transplant group and 20.3 years in the kidney transplant group (age data are available for 18 donors) [Table 1].

Efficacy Results:

Nine patients experienced one acute rejection episode in this study. In the heart transplant group, 5 patients had rejections with 2 classified as a BPAR. In the liver transplant group, 3 patients had rejections and all were classified as BPAR. In the kidney transplant group, 1 single patient had a rejection which was not classified as a BPAR [Table 2].

Thirteen patients experienced rejections during either Study F506CL-0403 or F506-CL-0404A.

There were no deaths.

Two patients with liver transplant experienced graft losses due to portal vein thrombosis and transplant failure after hepatic artery thrombosis (reported term was liver graft failure), 2 and 12 days, respectively, after being

enrolled in this extension study while continually receiving Modigraf. These 2 graft losses were considered to be not related to Modigraf by the Investigator.

Safety Results:

Overall, 43 (91.5%) patients reported at least 1 TEAE. The most commonly reported TEAEs were vomiting (15 [31.9%] patients) followed by diarrhea (14 [29.8%] patients), hypomagnesemia (11 [23.4%] patients) and hypertension (10 [21.3%] patients) [Table 3 and Table 4].

Overall, 32 (68.1%) patients reported at least 1 drug-related TEAE. The most commonly reported drug-related TEAEs were hypomagnesemia (8 [17.0%] patients) followed by hypertension (7 [14.9%] patients).

Overall, 26 (55.3%) patients reported at least 1 serious TEAE. The most commonly reported serious TEAE was gastroenteritis (4 [8.5%] patients) [Table 5].

Overall 3 (6.4%) patients reported a drug-related TEAE resulting in discontinuation.

The incidence of TEAEs was 31 (93.9%) in patients < 5 years and 12 (85.7%) in patients ≥ 5 years, respectively.

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

There were no deaths.

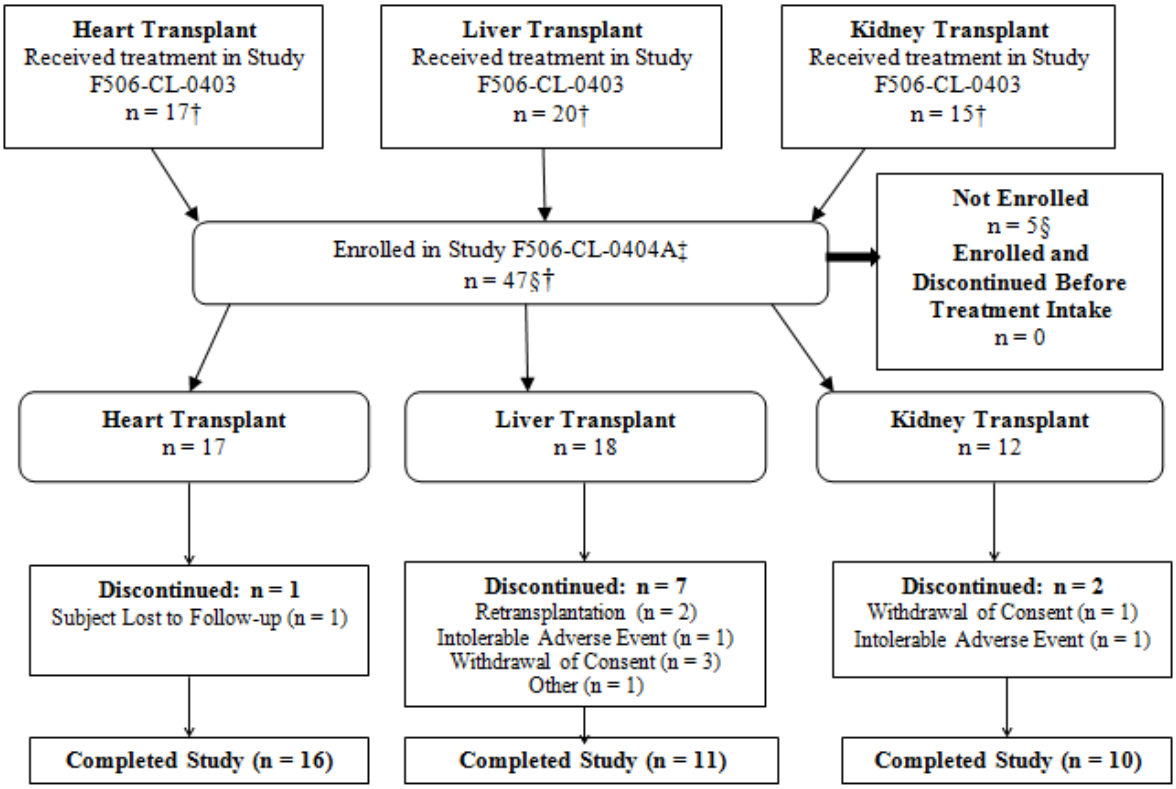
CONCLUSIONS:

Few rejections were observed in this extension study. Two patients with liver transplant experienced graft losses, which were reported as not related to Modigraf and no deaths occurred.

In this study, tacrolimus granules (Modigraf) had an acceptable safety profile and were well-tolerated when used in stable pediatric allograft recipients for up to 12 months. The numbers of TEAEs and SAEs were not unexpected in this transplanted population. The observed safety profile is consistent with the known characteristics of tacrolimus and no new safety issues were identified.

Date of Report: 01 Apr 2016

Figure 1 Disposition of Patients



† Data from Clinical Study Report F506-CL-0403.

‡ Patients were considered enrolled in Study F506-CL-0404A once the informed consent for this study had been completed.

§ Five patients who received treatment in Study F506-CL-0403 were not enrolled in this extension Study F506-CL-0404A; 3 of 5 patients discontinued Study F506-CL-0403 (2 withdrew consent and 1 started prohibited concomitant medication) and 2 of 5 patients completed Study F506-CL-0403.

Source: Tables 12.1.1.1, 12.1.1.3.1 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 = 18)	Kidney Transplant (n = 12)	Total (n = 47)
Sex, n (%) (Recipient)				
Male	13 (76.5%)	10 (55.6%)	9 (75.0%)	32 (68.1%)
Female	4 (23.5%)	8 (44.4%)	3 (25.0%)	15 (31.9%)
Sex, n (%) (Donor)				
Male	8 (47.1%)	8 (44.4%)	8 (66.7%)	24 (51.1%)
Female	8 (47.1%)	10 (55.6%)	4 (33.3%)	22 (46.8%)
Missing	1 (5.9%)	0	0	1 (2.1%)
Race, n (%) (Recipient)				
White	17 (100.0%)	18 (100.0%)	11 (91.7%)	46 (97.9%)
Black or African American	0	0	0	0
Asian	0	0	1 (8.3%)	1 (2.1%)
Other	0	0	0	0
Recipient Age at Transplantation (Years)				
n	17	18	12	47
Mean (SD)	5.2 (4.1)	2.3 (2.8)	5.3 (3.0)	4.1 (3.6)
Recipient Age at Enrollment (Years)				
n	17	18	12	47
Mean (SD)	5.3 (4.1)	2.3 (2.8)	5.4 (3.0)	4.2 (3.6)
Recipient Age at Transplantation subgroup				
< 5 years	9 (52.9%)	16 (88.9%)	8 (66.7%)	33 (70.2%)
≥ 5 years	8 (47.1%)	2 (11.1%)	4 (33.3%)	14 (29.8%)
Recipient Age at Transplantation subgroup				
≥ 28 days to ≤ 23 months (Infants and Toddlers)	5 (29.4%)	12 (66.7%)	0	17 (36.2%)
≥ 2 years to ≤ 11 years (Children)	11 (64.7%)	6 (33.3%)	12 (100.0%)	29 (61.7%)
≥ 12 years to ≤ 17 years (Adolescents)	1 (5.9%)	0	0	1 (2.1%)
Donor Age (Years)				
n	10	5	3	18
Mean (SD)	7.0 (4.5)	39.8 (8.3)	20.3 (20.3)	18.3 (16.9)
Time Since Transplantation (Day)†				
n	17	18	12	47
Mean (SD)	15.6 (1.3)	14.7 (3.3)	17.8 (10.6)	15.8 (5.7)
Recipient Weight (kg)				
n	16	17	11	44
Mean (SD)	15.97 (8.90)	11.24 (6.61)	17.58 (5.95)	14.54 (7.72)
Recipient Height (cm)				
n	10	9	11	30
Mean (SD)	96.90 (26.90)	82.78 (15.97)	100.78 (14.47)	94.09 (20.66)

BMI: body mass index (weight [kg]/height [m^2]); max: maximum; min: minimum.

† Time since transplantation was defined as (date of first dose in the study) - (date of transplantation) + 1.

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 = 18)	Kidney Transplant (n = 12)
All Rejections	5 (29.4%)	3 (16.7%)	1 (8.3%)
BPARs	2 (11.8%)	3 (16.7%)	0
NonBPARs	3 (17.6%)	0	1 (8.3%)
Any Acute Rejection			
Spontaneously resolving Acute Rejections†	1 (5.9%)	0	0
Corticosteroid-sensitive Acute Rejections‡	3 (17.6%)	2 (11.1%)	0
Corticosteroid-resistant Acute Rejections§	0	1 (5.6%)	0
Other Acute Rejections	1 (5.9%)	0	1 (8.3%)
BPAR			
Spontaneously Resolving Acute Rejections†	0	0	0
Corticosteroid-sensitive Acute Rejections‡	2 (11.8%)	2 (11.1%)	0
Corticosteroid-resistant Acute Rejections§	0	1 (5.6%)	0
Other Acute Rejections	0	0	0

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

Number of patients and percentage of patients (%) experiencing one or more rejection episodes are shown.

† Spontaneously resolving rejections are defined as rejection episodes which were not treated with new or increased corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus dose change.

‡ Corticosteroid-sensitive rejections are defined as rejection episodes treated with new or increased corticosteroid medication only and which have resolved, irrespective of any tacrolimus dose change.

§ Corticosteroid-resistant rejections are defined as rejection episodes which did not resolve following treatment with corticosteroids. If a rejection episode was not treated with corticosteroids first, but only with antibodies, it will nevertheless be included in this category.

Source: Table 12.3.1.1

Table 3 Overview of TEAEs (SAF)

Incidence of TEAE	Heart Transplant n = 17 n (%)	Liver Transplant n = 18 n (%)	Kidney Transplant n = 12 n (%)	Total n = 47 n (%)
Any TEAE	16 (94.1%)	15 (83.3%)	12 (100.0%)	43 (91.5%)
Drug-related† TEAEs	9 (52.9%)	12 (66.7%)	11 (91.7%)	32 (68.1%)
Deaths	0	0	0	0
Serious TEAEs‡	8 (47.1%)	9 (50.0%)	9 (75.0%)	26 (55.3%)
Drug-related† Serious TEAEs‡	3 (17.6%)	2 (11.1%)	7 (58.3%)	12 (25.5%)
Deaths Resulting from AEs	0	0	0	0
TEAEs Leading to Discontinuation of Study Drug	0	1 (5.6%)	2 (16.7%)	3 (6.4%)
Drug-related† TEAEs Leading to Discontinuation of Study Drug	0	1 (5.6%)	2 (16.7%)	3 (6.4%)

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

† Possible or probable, as assessed by the investigator, or records where relationship is missing.

‡ Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of always serious terms, if any upgrade was done.

Source: Table 12.6.1.1.1

Table 4 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 = 18	Kidney Transplant n = 12	Total n = 47
Overall	**14 (82.4%)**	**15 (83.3%)**	**11 (91.7%)**	**40 (85.1%)**
Gastrointestinal Disorders	**5 (29.4%)**	**9 (50.0%)**	**8 (66.7%)**	**22 (46.8%)**
Vomiting	1 (5.9%)	8 (44.4%)	6 (50.0%)	15 (31.9%)
Diarrhoea	4 (23.5%)	3 (16.7%)	7 (58.3%)	14 (29.8%)
Infections and Infestations	**3 (17.6%)**	**7 (38.9%)**	**9 (75.0%)**	**19 (40.4%)**
Human herpes virus infection	0	6 (33.3%)	0	6 (12.8%)
Nasopharyngitis	0	1 (5.6%)	4 (33.3%)	5 (10.6%)
Gastroenteritis	2 (11.8%)	1 (5.6%)	1 (8.3%)	4 (8.5%)
Epstein-Barr virus infection	0	3 (16.7%)	0	3 (6.4%)
Upper respiratory tract infection	1 (5.9%)	0	2 (16.7%)	3 (6.4%)
Lower respiratory tract infection	0	0	2 (16.7%)	2 (4.3%)
Oral candidiasis	0	0	2 (16.7%)	2 (4.3%)
Urinary tract infection	0	0	2 (16.7%)	2 (4.3%)
Metabolism and Nutrition Disorders	**4 (23.5%)**	**9 (50.0%)**	**3 (25.0%)**	**16 (34.0%)**
Hypomagnesaemia	4 (23.5%)	6 (33.3%)	1 (8.3%)	11 (23.4%)
Metabolic acidosis	0	7 (38.9%)	0	7 (14.9%)
Hypokalaemia	0	2 (11.1%)	1 (8.3%)	3 (6.4%)
Hyponatraemia	0	0	2 (16.7%)	2 (4.3%)
Blood and Lymphatic System Disorders	**6 (35.3%)**	**6 (33.3%)**	**3 (25.0%)**	**15 (31.9%)**
Neutropenia	5 (29.4%)	3 (16.7%)	1 (8.3%)	9 (19.1%)
Anaemia	1 (5.9%)	4 (22.2%)	2 (16.7%)	7 (14.9%)
Respiratory, Thoracic And Mediastinal Disorders	**1 (5.9%)**	**3 (16.7%)**	**7 (58.3%)**	**11 (23.4%)**
Cough	1 (5.9%)	1 (5.6%)	7 (58.3%)	9 (19.1%)
Rhinorrhoea	1 (5.9%)	0	4 (33.3%)	5 (10.6%)
Pleural effusion	0	3 (16.7%)	0	3 (6.4%)
Vascular Disorders	**5 (29.4%)**	**3 (16.7%)**	**2 (16.7%)**	**10 (21.3%)**
Hypertension	5 (29.4%)	3 (16.7%)	2 (16.7%)	10 (21.3%)
General Disorders and Administration Site Conditions	**2 (11.8%)**	**3 (16.7%)**	**3 (25.0%)**	**8 (17.0%)**
Pyrexia	2 (11.8%)	3 (16.7%)	1 (8.3%)	6 (12.8%)
Device occlusion	0	0	2 (16.7%)	2 (4.3%)
Renal and Urinary Disorders	2 (11.8%)	3 (16.7%)	0	5 (10.6%)
Renal impairment	2 (11.8%)	3 (16.7%)	0	5 (10.6%)
Injury, Poisoning and Procedural Complications	**0**	**3 (16.7%)**	**0**	**3 (6.4%)**
Complications of transplanted liver	0	3 (16.7%)	0	3 (6.4%)
Investigations	**0**	**0**	**3 (25.0%)**	**3 (6.4%)**
Blood creatinine increased	0	0	3 (25.0%)	3 (6.4%)
Endocrine Disorders	0	2 (11.1%)	0	2 (4.3%)
Hypothyroidism	0	2 (11.1%)	0	2 (4.3%)
Immune System Disorders	**0**	**0**	**2 (16.7%)**	**2 (4.3%)**
Seasonal allergy	0	0	2 (16.7%)	2 (4.3%)
Surgical and Medical Procedures	**0**	**0**	**2 (16.7%)**	**2 (4.3%)**
Central venous catheter removal	0	0	2 (16.7%)	2 (4.3%)

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

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† Sorting order: descending by number of patients of total group by system organ class and within that descending by number of patients of total group by preferred term. In case of ties, alphabetical order is applied.

Within a system organ class, patients may have reported more than 1 preferred term.

Source: Table 12.6.1.13

Table 5 Incidence of Serious TEAEs (MedDRA v15.0) (SAF)

MedDRA v15.0 SOC Preferred Term†	Number of Patients, n (%) Treatment Heart Transplant n = 17	E	Liver Transplant n = 18	E	Kidney Transplant n = 12	E	Total n = 47	E
Overall	**8 (47.1%)**	**12**	**9 (50.0%)**	**18**	**9 (75.0%)**	**32**	**26 (55.3%)**	**62**
Infections and Infestations	**5 (29.4%)**	**6**	**1 (5.6%)**	**1**	**5 (41.7%)**	**18**	**11 (23.4%)**	**25**
Gastroenteritis	2 (11.8%)	2	1 (5.6%)	1	1 (8.3%)	1	4 (8.5%)	4
Lower respiratory tract infection	0	0	0	0	2 (16.7%)	2	2 (4.3%)	2
Urinary tract infection	0	0	0	0	2 (16.7%)	10	2 (4.3%)	10
Bacterial sepsis	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Cytomegalovirus infection	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Gastroenteritis clostridial	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Gastroenteritis norovirus	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Gastroenteritis viral	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Gastrointestinal protozoal infection	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Postoperative wound infection	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Respiratory tract infection	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Urinary tract infection bacterial	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Investigations	**0**	**0**	**1 (5.6%)**	**1**	**3 (25.0%)**	**4**	**4 (8.5%)**	**5**
Blood creatinine increased	0	0	0	0	1 (8.3%)	2	1 (2.1%)	2
Body temperature increased	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Hepatic enzyme increased	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Transaminases increased	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**3 (16.7%)**	**4**	**1 (8.3%)**	**1**	**4 (8.5%)**	**5**
Pleural effusion	0	0	2 (11.1%)	2	0	0	2 (4.3%)	2
Lung consolidation	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Pulmonary oedema	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Respiratory failure	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Blood and Lymphatic System Disorders	**3 (17.6%)**	**3**	**0**	**0**	**0**	**0**	**3 (6.4%)**	**3**
Neutropenia	2 (11.8%)	2	0	0	0	0	2 (4.3%)	2
Febrile neutropenia	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1

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MedDRA v15.0 SOC Preferred Term†	Number of Patients, n (%) Treatment Heart Transplant n = 17	E	Liver Transplant n = 18	E	Kidney Transplant n = 12	E	Total n = 47	E
General Disorders and Administration Site Conditions	**1 (5.9%)**	**1**	**1 (5.6%)**	**1**	**1 (8.3%)**	**1**	**3 (6.4%)**	**3**
Pyrexia	1 (5.9%)	1	1 (5.6%)	1	0	0	2 (4.3%)	2
Drug interaction	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Injury, Poisoning and Procedural Complications	**0**	**0**	**3 (16.7%)**	**4**	**0**	**0**	**3 (6.4%)**	**4**
Biliary anastomosis complication	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Complications of transplanted liver	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Gastrointestinal anastomotic leak	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Tibia fracture	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Cardiac Disorders	**1 (5.9%)**	**1**	**1 (5.6%)**	**2**	**0**	**0**	**2 (4.3%)**	**3**
Cardiac hypertrophy	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Supraventricular tachycardia	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Tachycardia	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Gastrointestinal Disorders	0	0	1 (5.6%)	1	1 (8.3%)	1	2 (4.3%)	2
Intra-abdominal haemorrhage	0	0	1 (5.6%)	1	1 (8.3%)	1	2 (4.3%)	2
Hepatobiliary Disorders	0	0	2 (11.1%)	3	0	0	2 (4.3%)	3
Cholangitis	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Hepatic vein thrombosis	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Liver disorder	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**0**	**2 (16.7%)**	**3**	**2 (4.3%)**	**3**
Acidosis	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Dehydration	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Hyponatraemia	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Nervous System Disorders	0	0	1 (5.6%)	1	1 (8.3%)	1	2 (4.3%)	2
Convulsion	0	0	1 (5.6%)	1	0	0	1 (2.1%)	1
Neurotoxicity	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Renal and Urinary Disorders	**1 (5.9%)**	**1**	**0**	**0**	**1 (8.3%)**	**1**	**2 (4.3%)**	**2**
Oliguria	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Renal impairment	1 (5.9%)	1	0	0	0	0	1 (2.1%)	1
Social circumstances	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Treatment noncompliance	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1
Surgical and Medical Procedures	**0**	**0**	**0**	**0**	**1 (8.3%)**	**1**	**1 (2.1%)**	**1**
Central venous catheter removal	0	0	0	0	1 (8.3%)	1	1 (2.1%)	1

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

Source: Table 12.6.1.6.1