Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Advagraf®		
Name of Active Ingredient: Tacrolimus		

SYNOPSIS

Title of Study: A multi-center, randomized, open-label, pilot and exploratory study investigating safety and efficacy in OPTIMIZEd dosing of Advagraf® kidney transplantation in Asia.

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 6 sites (4 in Korea and 2 in Taiwan)

Publication Based on the Study: None

Study Period:

Study Initiation Date (Date of First Enrollment): 26 Jun 2014

Study Completion Date (Date of Last Evaluation): 22 Dec 2016

Phase of Development: Phase 4

Objectives: The objectives of this study were:

- To compare renal function between patients receiving optimized dose Advagraf over 52 weeks after kidney transplantation and patients receiving standard dose Advagraf
- To obtain pilot results of safety and efficacy data in optimized dose Advagraf over 52 weeks after kidney transplantation compared with standard dose Advagraf

Methodology:

This was a multi-center, randomized, open-label, parallel-group comparative, pilot and exploratory study.

Patients were screened at screening visit after providing written informed consent. After the screening visit, patients who met the inclusion criteria and did not meet the exclusion criteria at screening were enrolled in the initial phase and received the study drug, Advagraf, until week 4. After the initial phase, patients who met the inclusion criteria and did not meet the exclusion criteria at week 4 were randomized at week 4 to 1 of 2 arms in an open-label manner:

- Arm 1: optimized dose of study drug
- Arm 2: standard dose of study drug

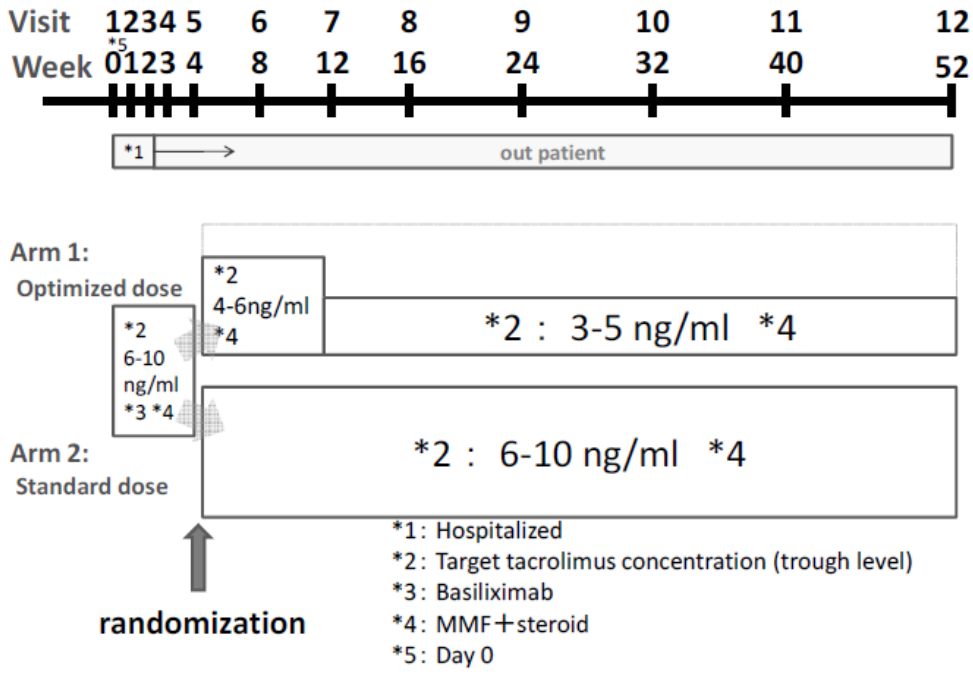
The administration period of study drug was 52 weeks including the initial phase.

After the initial dose of study drug at a dose of 0.2 to 0.3 mg/kg per day, patients were treated with study drug once daily aiming a tacrolimus trough level of 6 to 10 ng/mL during the 4-week initial phase.

After the initial phase, patients with a tacrolimus trough level at 6 to 10 ng/mL received either optimized dose (Arm 1) or standard dose (Arm 2) of study drug. Target tacrolimus trough level of Arm 1 was 4 to 6 ng/mL after week 4 until week 12 and was 3 to 5 ng/mL after week 12 until week 52. Target tacrolimus trough level of Arm 2 was 6 to 10 ng/mL until week 52.

An overview of the study design is shown in Figure 1.

Figure 1 Overview of the Study Design



Source: Appendix 13.1.1

Number of Patients (Planned, Enrolled and Analyzed):

Target number of patients: Total of 100 patients, consisting of 2 groups of over 45 patients each.

Number of patients enrolled: In total, 79 patients were enrolled and 74 patients received at least 1 prerandomization dose. Of 79 patients, 13 patients discontinued the study before randomization.

Analysis populations: The full analysis set (FAS) consisted of 32 patients in Arm 1 and 34 patients in Arm 2 and the safety analysis set (SAF) consisted of 32 patients in Arm 1 and 34 patients in Arm 2.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Patients meeting all of following inclusion criteria at day 0, were eligible for the study at screening visit:

1. Male or female patient between 20 to 65 years
2. End stage kidney disease and a suitable candidate for primary kidney transplantation or retransplantation (unless the graft was lost from rejection within 52 weeks)

3. Had received a kidney transplant from a deceased or living (non human leukocyte antigen [HLA] identical) donor with compatible ABO blood type
4. Female patient of childbearing potential had to have a negative serum or urine pregnancy test at enrollment and had to agree to maintain effective birth control during the study. Male patient of childbearing potential had to agree to maintain effective birth control during the study.
5. Patient had been fully informed and had signed an institutional review board/independent ethics committee approved informed consent form (ICF) and was willing and able to follow study procedures.

Exclusion Criteria

Patients meeting any of following exclusion criteria at day 0 and week 4 were going to be excluded from participating:

At Screening Visit:

1. Had received an organ transplant other than a kidney
2. Cold ischemia time of the donor kidney > 24 hours
3. Had received a graft from a nonheart-beating donor other than of Maastricht category 3 (withdrawal of support awaiting cardiac arrest)
4. Significant liver disease, defined as having continuously elevated alanine aminotransferase and/or aspartate aminotransferase and/or total bilirubin levels ≥ 2 times the upper value of the normal range of the investigational site
5. Had received a graft from a hepatitis C- or B-positive donor
6. Had required on-going dosing with a systemic immunosuppressive drug prior to transplantation (e.g., for Lupus disease, focal segmental glomerulonephritis, etc.) other than minimal levels of immunosuppressant following failure of a previous transplantation without nephrectomy
7. Significant, uncontrolled concomitant infections and/or severe diarrhea, vomiting, active upper gastro-intestinal tract malabsorption or active peptic ulcer
8. Patient or donor known to be human immunodeficiency virus (HIV) positive
9. Known allergy or intolerance to tacrolimus, macrolide antibiotics, steroids, lactose, basiliximab, mycophenolate mofetil or any of the product excipients
10. Patient had malignant tumor (except patient who did not have a recurrence of malignant tumor 5 or more years before the signature on ICF).
11. Currently participating in another clinical study and/or had taken an investigational drug within 12 weeks prior to the signature on ICF
12. Any form of substance abuse, psychiatric disorder or condition that, in the opinion of the investigator, could complicate communication with the investigator
13. Unlikely to comply with the visits scheduled in the protocol
14. Patient who had no plan to receive the induction therapy at the transplantation
15. Expanded criteria donor kidney (United Network for Organ Sharing/Organ Procurement and transplantation Network)
16. Patient with a high immunological risk, defined as:
    1) A panel reactive antibody (PRA) level > 50% in the previous 52 weeks
    2) Donor specific antibodies (DSA) positive before the transplantation
    3) T and/or B cell cross-match positive before the transplantation
    4) Patients with a previous graft loss < 52 weeks due to immunological reasons

At Week 4:*

Patients meeting any of following criteria at week 4, were going to be excluded from participating:

1. Patient who did not receive the basiliximab induction therapy at the time of transplantation
2. Patient whose dose adjustment after week 4 was judged to be contra-indicated by the investigator due to a recent rejection episode such as treatment finished within 7 days
3. Cold ischemia time of the donor kidney > 24 hours
4. Patient who had delayed graft function (patient required more than one dialysis treatment in the first week following transplantation)
5. Patient whose pretransplant DSA result was found to be positive

*: An investigator had to exclude the patients from the study between day 0 and week 4, once the investigator found the patient fitted with 1 of 5 exclusion criteria above.

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

Advagraf prolonged-release hard capsules were administered orally once daily.

They were supplied in the following strengths: 0.5 mg (lot No.: [redacted]), 1 mg (lot No.: [redacted]) and 5 mg (lot No.: [redacted]).

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

52 weeks

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

Not used in this study

Criteria for Evaluation:

Efficacy Variables

Primary Efficacy Variable

The primary efficacy variable was the estimated glomerular filtration rate (eGFR) over 52 weeks.

The eGFR was assessed by modified modification of diet in renal disease (MDRD) formula.

Modified MDRD method (mL/min per 1.73 m^2):

For Korean patients:

$175 \times \text{serum creatinine (SCr)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if woman)

For Taiwanese patients:

$175 \times \text{SCr}^{-1.234} \times \text{Age}^{-0.179} \times 0.79$ (if woman)

Secondary Efficacy Variables

- Calculated creatinine clearance at week 52
- SCr value at week 52
- Graft survival at week 52

- Patient survival at week 52
- Biopsy proven acute rejection (BPAR) at week 52
    - Incidence of BPAR
    - Severity of BPAR
- Composite of graft loss, patient death and BPAR at week 52
- Acute rejection
    - Incidence of acute rejection
    - Time to first acute rejection
    - Multiple rejection
- Steroid-resistant acute rejection
    - Incidence of steroid-resistant acute rejection
    - Time to first steroid-resistant acute rejection

Safety Variables

- Adverse events (AEs) (treatment-emergent adverse events [TEAEs])
    - Frequency
    - Severity
    - Seriousness
    - Relationship to study drug
- Vital signs/Weight
    - Systolic and diastolic blood pressure
    - Pulse rate
    - Weight
- Laboratory assessments
    - Hematology
    - Biochemistry
    - Absolute change in serum lipids
    - Urinalysis
    - Pregnancy test
    - Biomarkers

Statistical Methods:

Efficacy

Primary Variable

The primary efficacy analysis was performed on the FAS.

eGFR was summarized by treatment group and visit using descriptive statistics.

The primary analysis was performed on the eGFR over 52 weeks. Patients without any postbaseline eGFR assessment were not included in this analysis.

The following hypotheses were constructed:

H_0: There was no significant difference of the mean value of eGFR between the optimized dosing of study drug and standard dosing of study drug.

H_1: There was the significant difference of the mean value of eGFR between the optimized dosing of study drug and standard dosing of study drug.

The two-sided p-values for the hypothesis tests were calculated, together with the 95% confidence intervals.

Secondary Variables

Analyses of the secondary efficacy variables were performed for the FAS.

All secondary variables were summarized per treatment group using appropriate descriptive statistics. Where appropriate, summaries were provided over time.

Safety

AEs that newly occurred or were worsened during the period from the day 0 to before randomization, from randomization to end of treatment and from week 12 to end of treatment were summarized and analyzed for each treatment group. Other variables were analyzed by descriptive statistics.

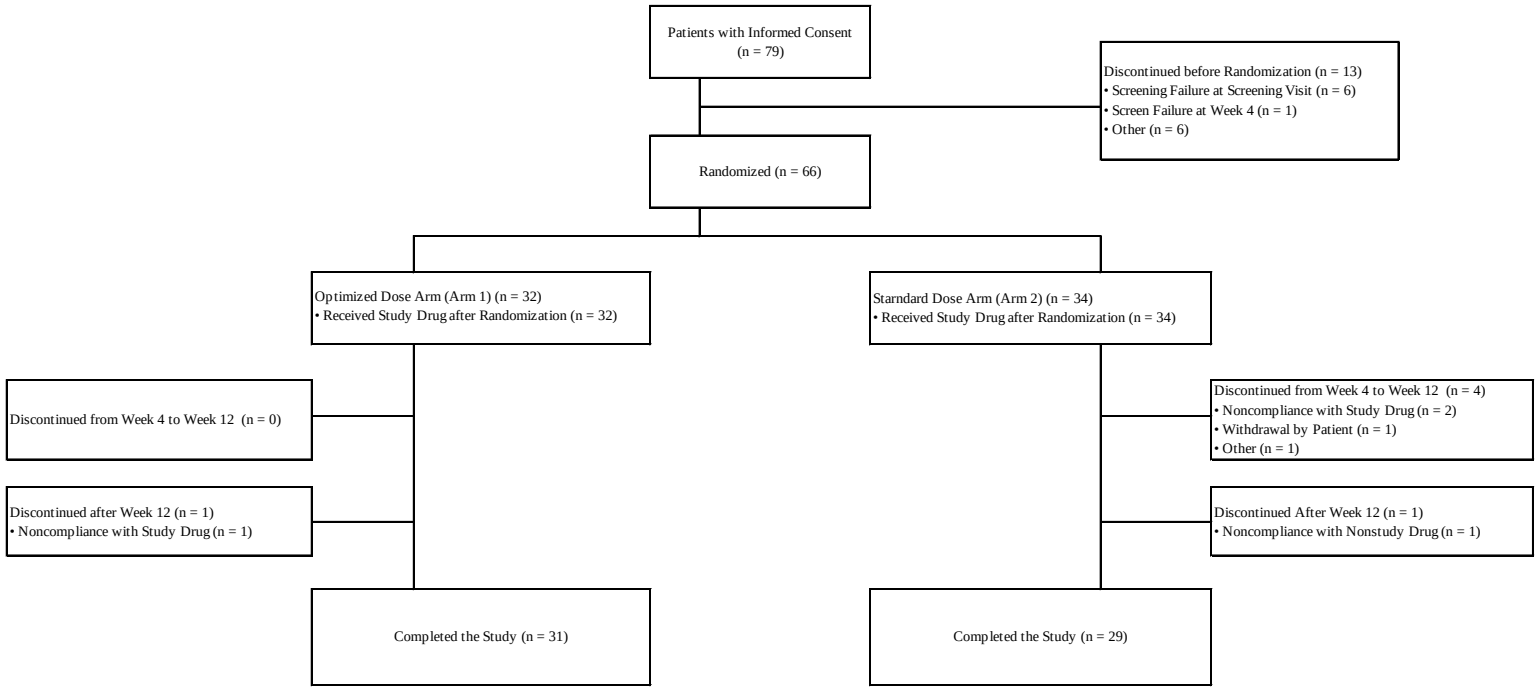
Summary of Results/Conclusions:

Study Population

In this study, 79 patients were enrolled and 66 patients (32 patients in Arm 1 and 34 patients in Arm 2) were randomized and all of them received the study drug after randomization. A total of 60 patients (31 patients in Arm 1 and 29 patients in Arm 2) completed the study, while 4 patients (all in Arm 2) discontinued the study between week 4 and week 12 and 2 patients (1 patient in Arm 1 and 1 patient in Arm 2) discontinued the study after week 12. Common reasons for the discontinuation from the study between week 4 and week 12 included noncompliance with study drug and withdrawal by patient. Common reasons for the discontinuation from the study after week 12 included noncompliance with study drug and noncompliance with nonstudy drug [Figure 2; Figure 3]. The proportion of patients staying on study drug treatment was numerically higher in Arm 1 (96.9% [31/32]) than Arm 2 (85.3% [29/34]) [Figure 4].

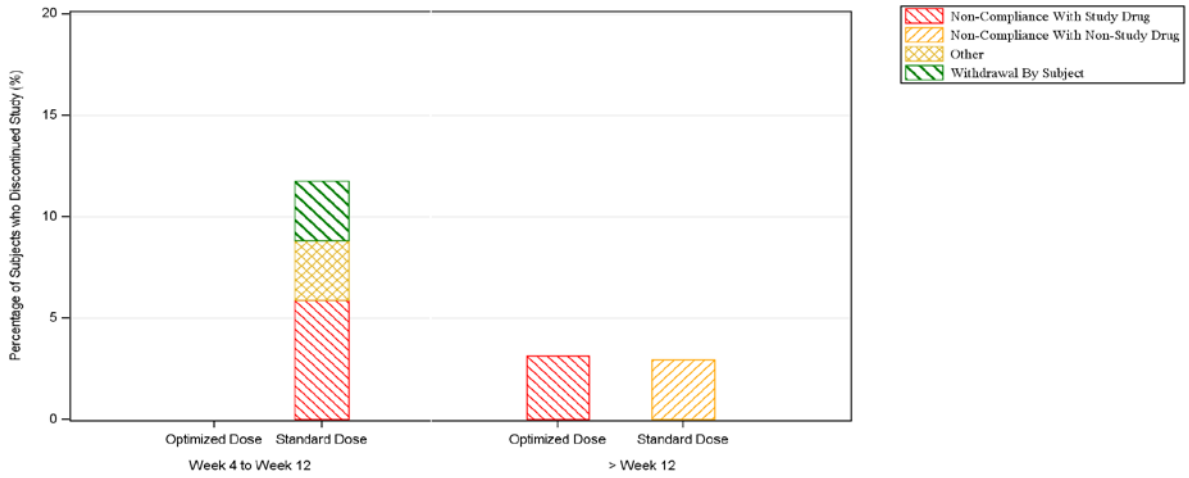
Of the 66 patients included in the FAS, 44 patients (66.7%) were men and 22 patients (33.3%) were women. The mean age was 45.5 years. The numbers of HLA total A + B + DR mismatches were 0 for 2 patients (3.0%), 1 for 4 patients (6.1%), 2 for 15 patients (22.7%), 3 for 20 patients (30.3%), 4 for 12 patients (18.2%), 5 for 9 patients (13.6%) and 6 for 4 patients (6.1%). The demographic and other baseline characteristics were similar in each treatment arm [Table 1]. The most common reasons for kidney failure were other in 14 patients (21.2%) and unknown in 13 patients (19.7%). Additional reasons for kidney failure were immunoglobulin A nephropathy in 9 patients (13.6%), and diabetic nephropathy and hypertensive nephrosclerosis (including hypertensive nephropathy) in 8 patients (12.1% each).

Figure 2 Patient Disposition (All Patients with Informed Consent)



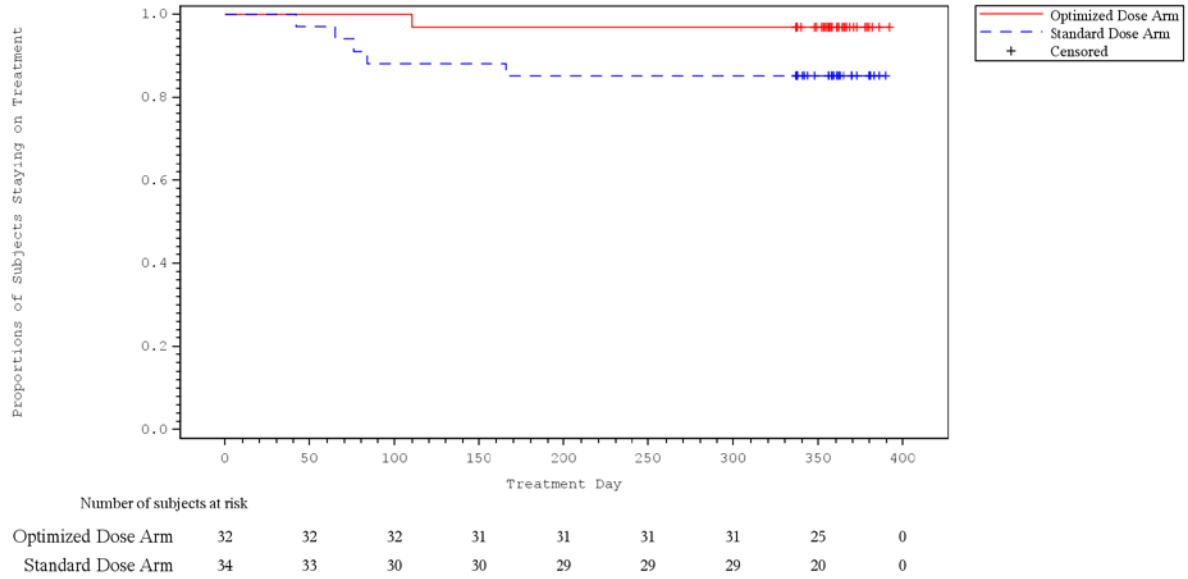
Source: Table 12.1.1.1, Table 12.1.1.2, Table 12.1.1.4.1, Table 12.1.1.4.2, Table 12.1.1.5.1 and Table 12.1.1.5.2

Figure 3 **Bar Chart of Treatment Discontinuation by Reason (SAF)**



Source: Figure 12.1.1.1

Figure 4 **Kaplan-Meier Plot of Time to Treatment Discontinuation (FAS)**



Source: Figure 12.3.9.1

Table 1 **Demographic and Baseline Characteristics of Patients (FAS)**

Parameter	Category/ Statistic	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Sex	Male	21 (65.6%)	23 (67.6%)	44 (66.7%)
	Female	11 (34.4%)	11 (32.4%)	22 (33.3%)
Race	Asian	32 (100.0%)	34 (100.0%)	66 (100.0%)
	Other	0	0	0
Race Sub-category for Asian	Korean	31 (96.9%)	32 (94.1%)	63 (95.5%)
	Taiwanese	1 (3.1%)	2 (5.9%)	3 (4.5%)
	Other	0	0	0

Table continued on next page

Parameter	Category/ Statistic	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Age (years)	n	32	34	66
	Mean	44.5	46.6	45.5
	SD	11.1	10.2	10.6
	Min	20	20	20
	Median	46.5	49.0	47.5
	Max	65	63	65
Age Group (years)	< 65	31 (96.9%)	34 (100.0%)	65 (98.5%)
	≥ 65	1 (3.1%)	0	1 (1.5%)
Weight (kg)	n	32	34	66
	Mean	67.73	62.05	64.80
	SD	15.37	12.86	14.31
	Min	39.7	38.7	38.7
	Median	68.35	61.15	63.55
	Max	100.6	98.5	100.6
Height (cm)	n	32	34	66
	Mean	165.43	164.84	165.13
	SD	9.15	9.76	9.40
	Min	148	143.7	143.7
	Median	165.35	165.35	165.35
	Max	183.9	184.1	184.1
BMI (kg/m^2)	n	32	34	66
	Mean	24.479	22.629	23.526
	SD	3.912	3.011	3.574
	Min	18.12	17.78	17.78
	Median	24.254	22.194	22.364
	Max	32.30	32.24	32.30
HIV	Negative	32 (100.0%)	34 (100.0%)	66 (100.0%)
	Positive	0	0	0
HBV (HBsAg)	Negative	32 (100.0%)	32 (94.1%)	64 (97.0%)
	Positive	0	2 (5.9%)	2 (3.0%)
HCV (anti-HCV IgG)	Negative	32 (100.0%)	34 (100.0%)	66 (100.0%)
	Positive	0	0	0
CMV (anti-CMV IgG)	Negative	1 (3.3%)	0	1 (1.6%)
	Positive	29 (96.7%)	34 (100.0%)	63 (98.4%)
	Missing	2	0	2
EBV (anti-VCA IgG)	Negative	3 (9.7%)	1 (3.0%)	4 (6.3%)
	Positive	28 (90.3%)	32 (97.0%)	60 (93.8%)
	Missing	1	1	2
ABO Type Mismatch	Yes	0	0	0
	No	32 (100.0%)	34 (100.0%)	66 (100.0%)
HLA Total A+B+DR Mismatches	0	2 (6.3%)	0	2 (3.0%)
	1	1 (3.1%)	3 (8.8%)	4 (6.1%)
	2	6 (18.8%)	9 (26.5%)	15 (22.7%)
	3	11 (34.4%)	9 (26.5%)	20 (30.3%)
	4	5 (15.6%)	7 (20.6%)	12 (18.2%)
	5	5 (15.6%)	4 (11.8%)	9 (13.6%)
	6	2 (6.3%)	2 (5.9%)	4 (6.1%)

Table continued on next page

Parameter	Category/ Statistic	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
PRA Grade (or Equivalent) (%)	n	32	34	66
	Mean	5.06	3.19	4.10
	SD	11.73	7.45	9.73
	Min	0	0	0
	Median	0.00	0.00	0.00
	Max	47	30	47

BMI: body mass index; CMV: cytomegalovirus; DR: D-related; EBV: Epstein Barr virus; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; IgG: immunogloblin G; Max: maximum; Min: minimum; N: number of patients in each arm; n: number of patients; PRA: panel reactive antibody; VCA: viral capsid antigen.
Source: Table 12.1.2.1.1 and Table 12.1.2.4.1

Treatment Compliance and Study Drug Exposure

The mean duration of treatment was 336.2 days for total patients, 352.8 days in Arm 1 and 320.6 days in Arm 2. The mean treatment compliance rate was 97.64% for total patients, 98.29% in Arm 1 and 97.03% in Arm 2. There were no notable differences between treatment arms in duration of treatment or treatment compliance [Table 2]. The daily dose of study drug was similar in Arm 1 and Arm 2 until the first dose adjustment at week 4, and was greater in Arm 2 after the first and second dose adjustments at week 4 and week 12, respectively, due to the difference in the treatment regimens [Figure 5]. The mean of tacrolimus trough level over 52 weeks was also similar in Arm 1 and Arm 2 until the first dose adjustment at week 4, and was greater in Arm 2 after the first and second dose adjustments at week 4 and week 12, respectively. The target tacrolimus trough level was met in both Arm 1 and Arm 2 at the majority of the time points [Figure 6].

Table 2 Study Drug Exposure – Overall (FAS)

Characteristic		Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Duration (days) [1]	n	32	34	66
	Mean	352.8	320.6	336.2
	SD	46.7	100.5	80.2
	Min	109	43	43
	Median	358.0	357.0	357.5
	Max	392	389	392
Total Test Drug Used (mg) [2]	n	32	34	66
	Mean	1896.14	2380.78	2145.80
	SD	634.93	1583.03	1234.55
	Min	741.5	149.5	149.5
	Median	1897.00	1952.50	1952.50
	Max	3414.0	6065.0	6065.0
Average Daily Dose (mg) [3]	n	32	34	66
	Mean	5.69	7.17	6.45
	SD	3.02	4.07	3.65
	Min	2.1	2.0	2.0
	Median	5.26	5.65	5.54
	Max	19.1	16.9	19.1
Dosing [4]	Increases	2 (6.3%)	0	2 (3.0%)
	Decreases	2 (6.3%)	5 (14.7%)	7 (10.6%)
	Interruptions	1 (3.1%)	0	1 (1.5%)

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Characteristic		Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Treatment Compliance (%) [5]	n	32	34	66
	Mean	98.29	97.03	97.64
	SD	15.75	12.78	14.20
	Min	39.7	53.9	39.7
	Median	100.00	99.84	99.98
	Max	146.0	117.7	146.0
Treatment Compliance Category (%)	< 50	1 (3.1%)	0	1 (1.5%)
	≥ 50 to ≤ 75	0	3 (8.8%)	3 (4.5%)
	> 75	31 (96.9%)	31 (91.2%)	62 (93.9%)

Max: maximum; Min: minimum; N: number of patients in each arm; n: number of patients contributed to the analysis; SD: standard deviation.

[1] Duration was defined as (the date of last dosing) - (the date of first dosing) + 1; duration for the visit n was defined as (the date of visit n) - (the date of the visit n - 1).

[2] Total test drug used = (total drug disposed) - (total drug returned) - (total drug lost); test drug used at visit n = (drug disposed at visit n - 1) - (drug returned at visit n) - (drug lost at visit n).

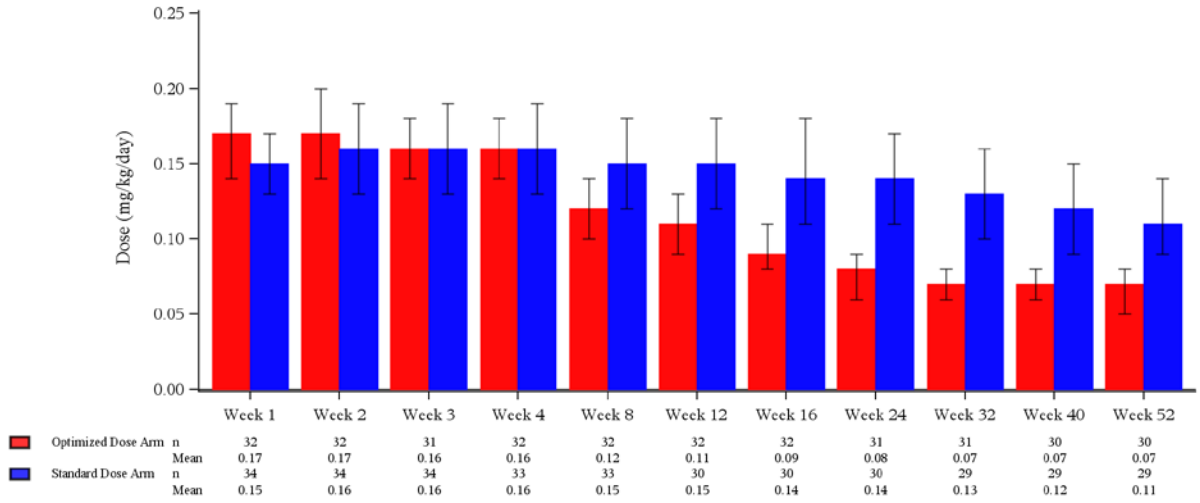
[3] Average daily dose = (total test drug used)/(duration); daily dose at visit n = (test drug used at visit n)/(duration for the visit n).

[4] Only dosing change resulted by adverse events are shown.

[5] Treatment compliance = (total prescribed [mg] - total returned [mg] - total lost [mg])/(total amount should be taken [mg]) × 100.

Source: Table 12.2.1.1.1.1

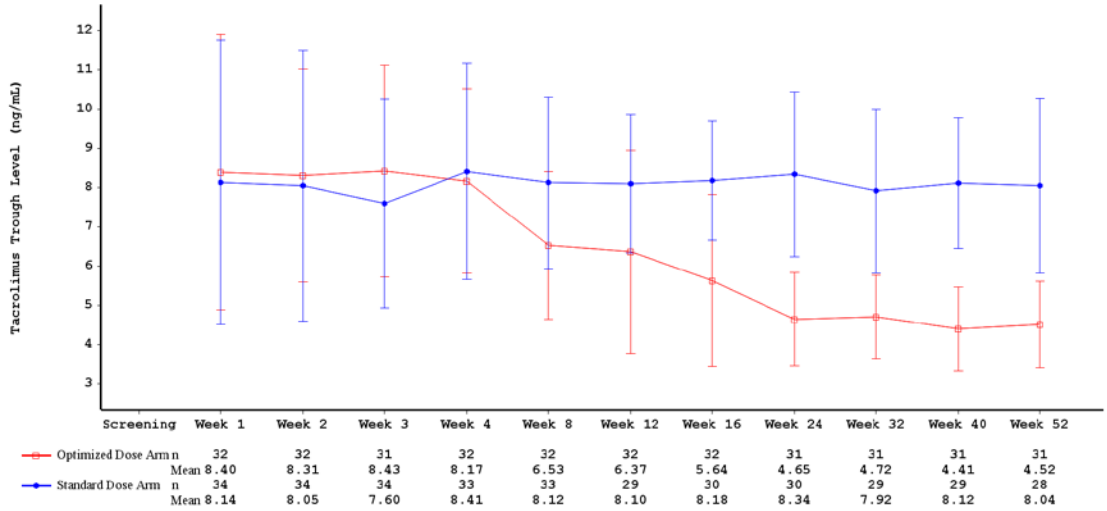
Figure 5 Bar Chart of Daily Dose (FAS)



n: number of patients contributed to the analysis.

Source: Figure 12.2.1

Figure 6 Line Plot of Tacrolimus Trough Level (FAS)



n: number of patients contributed to the analysis.
Source: Figure 12.2.2

Efficacy Results:

The efficacy of the optimized dosing regimen was analyzed in the FAS. The primary variable, eGFR over 52 weeks, was compared based on a repeated measures analysis of covariance mixed model with treatment arms, donor type (deceased or living) and scheduled visit as factors and eGFR at week 4 as a covariate, with variance-covariance structure set to unstructured. Although there was a trend showing eGFR was numerically lower in Arm 1 than Arm 2 after randomization, the analysis revealed no significant differences between treatment arms in the eGFR value from week 8 to week 52 (P = 0.272). The same model was performed by including the treatment-by-visit interaction into the model, and the analysis revealed no significant interactions between treatment arms and the time points (P = 0.812), and thus primary analysis model did not include the interaction term [Table 3; Figure 7].

Subgroup analysis of the primary variable was performed on patients transplanted from living donor in the FAS. The analysis revealed no significant differences between treatment arms in the eGFR value from week 8 to week 52 (P = 0.394) and no significant interactions between treatment arms and time points (P = 0.844) [Table 4].

The comparisons of primary variable at each scheduled visit in the FAS were based on ANCOVA with treatment arms and donor type (deceased or living) as fixed categorical effects and eGFR at week 4 as a covariate. The result of this secondary analysis was similar to the primary analysis.

The comparison of secondary variables revealed no significant differences between treatment arms in calculated creatinine clearance, SCr, graft and patient survival, rate of BPAR-free, rate of composite event-free, incidence rate of acute rejection including steroid-resistant acute rejection and multiple acute rejections, or incidence rate and severity of BPAR.

Table 3 Comparison of eGFR Based on Repeated Measures Analysis Over 52 Weeks (FAS)

Visit	Statistic	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)
Week 8 (Visit 6)	n	32	33
	LS mean	65.20	68.03
	95% CI of LS mean	61.34, 69.07	64.21, 71.84
Week 12 (Visit 7)	n	32	30
	LS mean	64.48	67.30
	95% CI of LS mean	60.51, 68.44	63.35, 71.25
Week 16 (Visit 8)	n	32	30
	LS mean	65.90	68.72
	95% CI of LS mean	61.36, 70.44	64.24, 73.21
Week 24 (Visit 9)	n	31	30
	LS mean	64.06	66.88
	95% CI of LS mean	59.81, 68.31	62.64, 71.13
Week 32 (Visit 10)	n	31	29
	LS mean	65.46	68.29
	95% CI of LS mean	61.70, 69.23	64.48, 72.09
Week 40 (Visit 11)	n	31	29
	LS mean	65.10	67.93
	95% CI of LS mean	61.11, 69.10	63.90, 71.95
Week 52 (Visit 12)	n	31	28
	LS mean	68.47	71.29
	95% CI of LS mean	64.20, 72.74	66.99, 75.59
Overall Difference [1]	LS mean	−2.82	
	95% CI of LS mean	−7.91, 2.27	
	P value	0.272	
Treatment-by-visit	P value	0.812	

The unit of eGFR is mL/min per 1.73 m².

The comparison was based on a repeated measures analysis of covariance mixed model with treatment arms, donor type (deceased or living), and scheduled visit as factors and eGFR at week 4 as a covariate, with variance-covariance structure set to unstructured.

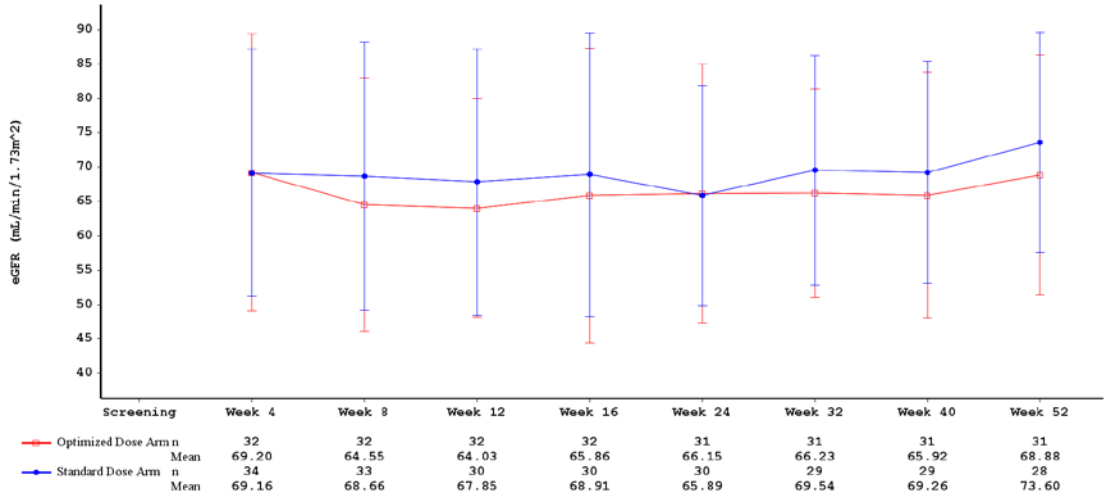
The scheduled visits after randomization (week 4) were week 8, week 12, week 16, week 24, week 32, week 40 and week 52.

CI: confidence interval; eGFR: estimated glomerular filtration rate; LS: least squares; N: number of patients in each arm; n: number of patients contributed to the analysis.

[1] Difference = optimized dose arm - standard dose arm.

Source: Table 12.3.1.1

Figure 7 **Line Plot of the Observed eGFR Value Over 52 Weeks (FAS)**



n: number of patients contributed to the analysis.

Source: Table 12.3.3.1

Table 4 **Comparison of eGFR Based on Repeated Measures Analysis Over 52 Weeks for Subgroup of Living Donor (FAS)**

Visit	Statistic	Optimized Dose Arm (N = 31)	Standard Dose Arm (N = 31)
Week 8 (Visit 6)	n	31	30
	LS mean	65.79	68.08
	95% CI of LS mean	61.82, 69.76	64.05, 72.11
Week 12 (Visit 7)	n	31	27
	LS mean	64.61	66.90
	95% CI of LS mean	60.54, 68.67	62.74, 71.06
Week 16 (Visit 8)	n	31	27
	LS mean	66.25	68.54
	95% CI of LS mean	61.51, 70.99	63.76, 73.32
Week 24 (Visit 9)	n	30	27
	LS mean	64.25	66.54
	95% CI of LS mean	59.81, 68.68	62.01, 71.07
Week 32 (Visit 10)	n	30	26
	LS mean	65.18	67.47
	95% CI of LS mean	61.27, 69.09	63.41, 71.53
Week 40 (Visit 11)	n	30	26
	LS mean	64.81	67.10
	95% CI of LS mean	60.64, 68.97	62.80, 71.40
Week 52 (Visit 12)	n	30	25
	LS mean	67.81	70.10
	95% CI of LS mean	63.40, 72.22	65.57, 74.64
Overall Difference [1]	LS mean	−2.29	
	95% CI of LS mean	−7.64, 3.05	
	P value	0.394	
Treatment-by-visit	P value	0.844	
Footnotes appear on next page			

The unit of eGFR was mL/min per 1.73 m².

The comparison was based on repeated measures analysis of covariance mixed model with treatment arms and scheduled visit as factors, and eGFR at week 4 as covariate, with varience-covariance structure set to unstructured.

The scheduled visits after randomization (week 4) were week 8, week 12, week 16, week 24, week 32, week 40 and week 52.

CI: confidence interval; eGFR: estimated glomerular filtration rate; LS: least squares; N: number of patients in each arm; n: number of patients contributed to the analysis.

[1] Difference = optimized dose arm - standard dose arm.

Source: Table 12.3.1.2

Safety Results:

AEs and TEAEs in the initial phase and postrandomization period were summarized for patients in the SAF for both treatment arms. TEAEs were reported for all patients (100.0%) in both treatment arms. Drug-related TEAEs were reported for 34.4% (11/32) of patients in Arm 1 and 38.2% (13/34) of patients in Arm 2. No deaths or TEAEs leading to permanent discontinuation of study drug occurred in any treatment arms. Serious TEAEs were reported for 34.4% (11/32) of patients in Arm 1 and 38.2% (13/34) of patients in Arm 2. Drug-related serious TEAEs were reported for 6.3% (2/32) of patients in Arm 1 and 8.8% (3/34) of patients in Arm 2 [Table 5].

The most frequently reported (≥ 5% of patients in either treatment arm) TEAEs (including SAEs) were hyperkalaemia (19.7%), and constipation, nasopharyngitis, hyperlipidaemia and insomnia (18.2% each) for total patients, constipation and hyperkalaemia (25.0% each), and nasopharyngitis and insomnia (21.9% each) in Arm 1, and hyperlipidaemia (20.6%) and diarrhoea (17.6%) in Arm 2. There were no notable differences in the safety events between treatment arms [Table 6].

The most frequently reported serious TEAEs were blood creatinine increased (9.1%) and transplant rejection (7.6%) for total patients, transplant rejection and blood creatinine increased (6.3% each) in Arm 1, and blood creatinine increased (11.8%) and transplant rejection (8.8%) in Arm 2 [Table 7].

There were no notable differences in the safety events between treatment arms.

At baseline, laboratory test results for erythrocytes, hematocrit and hemoglobin were below the reference range for at least 78.1% of patients in both treatment arms. These parameters improved over time in both treatment arms up to week 52. At week 52, the laboratory test results for erythrocytes, hematocrit and hemoglobin were below the reference range for at most 19.4% of patients in both treatment arms. At baseline, the laboratory test result for leukocytes was above the reference range for at most 25.0% of patients in both treatment arms. It improved over time in Arm 1 up to week 52. At week 52, the laboratory test result for leukocytes was above the reference range for at most 16.1% of patients in both treatment arms. However, at least 17.4% of patients in both treatment arms who had normal leukocytes at baseline were reported to be below or above the reference range at week 52. At baseline, laboratory test for creatinine was above the reference range for all patients. It improved over time in both treatment arms up to week 52. At week 52, laboratory test result for creatinine was above the reference range in for most 29.0% of patients in both treatment arms.

There were no notable differences between treatment arms in other hematology, biochemistry or urinalysis parameters, DSA at week 52 or vital signs/weight.

Table 5 Overview of AEs (SAF)

	Optimized Dose Arm (N = 32) n (%) #E	**Standard Dose Arm (N = 34) n (%) #E**	**Total (N = 66) n (%) #E**
Adverse Events	32 (100.0%) 182	34 (100.0%) 172	66 (100.0%) 354
Serious Adverse Events [1]	11 (34.4%) 14	13 (38.2%) 19	24 (36.4%) 33
Treatment-emergent Adverse Events	32 (100.0%) 178	34 (100.0%) 168	66 (100.0%) 346
Drug-related Treatment-emergent Adverse Events [2]	11 (34.4%) 21	13 (38.2%) 16	24 (36.4%) 37
Serious Treatment-emergent Adverse Events [1]	11 (34.4%) 14	13 (38.2%) 19	24 (36.4%) 33
Drug-related Serious Treatment-emergent Adverse Events [1] [2]	2 (6.3%) 3	3 (8.8%) 4	5 (7.6%) 7
Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Study Drug	0	0	0
Death	0	0	0

The events, both in the initial phase and postrandomization period, are presented.

#E: number of events; %: percentage of patients; N: number of patients in each arm; n: number of patients.

[1] Included serious adverse events upgraded by the sponsor based on review of the sponsor's list of always serious terms, if any upgrade was done.

[2] Possible or probable, as assessed by the investigator, or records where relationship was missing.

Source: Table 12.6.1.1.4

Table 6 TEAEs Reported in at Least 5% of Patients in Any Treatment Arm by SOC and Preferred Term (MedDRA Version 16.1) (SAF)

MedDRA (v16.1) System Organ Class Preferred Term	**Optimized Dose Arm (N = 32)**	**Standard Dose Arm (N = 34)**	**Total (N = 66)**
Overall	32 (100.0%)	34 (100.0%)	66 (100.0%)
Blood and lymphatic system disorders	5 (15.6%)	3 (8.8%)	8 (12.1%)
Anaemia	5 (15.6%)	2 (5.9%)	7 (10.6%)
Gastrointestinal disorders	18 (56.3%)	14 (41.2%)	32 (48.5%)
Constipation	8 (25.0%)	4 (11.8%)	12 (18.2%)
Diarrhoea	1 (3.1%)	6 (17.6%)	7 (10.6%)
Dyspepsia	3 (9.4%)	3 (8.8%)	6 (9.1%)
Nausea	4 (12.5%)	1 (2.9%)	5 (7.6%)
Vomiting	1 (3.1%)	2 (5.9%)	3 (4.5%)
General disorders and administration site conditions	4 (12.5%)	3 (8.8%)	7 (10.6%)
Pyrexia	0	2 (5.9%)	2 (3.0%)
Immune system disorders	3 (9.4%)	3 (8.8%)	6 (9.1%)
Transplant rejection	2 (6.3%)	3 (8.8%)	5 (7.6%)
Infections and infestations	15 (46.9%)	16 (47.1%)	31 (47.0%)
BK virus infection	2 (6.3%)	5 (14.7%)	7 (10.6%)
Cytomegalovirus infection	0	2 (5.9%)	2 (3.0%)
Herpes simplex	0	2 (5.9%)	2 (3.0%)
Influenza	1 (3.1%)	2 (5.9%)	3 (4.5%)
Nasopharyngitis	7 (21.9%)	5 (14.7%)	12 (18.2%)
Oral herpes	2 (6.3%)	1 (2.9%)	3 (4.5%)
Urinary tract infection	1 (3.1%)	2 (5.9%)	3 (4.5%)

Table continued on next page

MedDRA (v16.1) System Organ Class Preferred Term	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Injury, poisoning and procedural complications	6 (18.8%)	5 (14.7%)	11 (16.7%)
Procedural pain	2 (6.3%)	3 (8.8%)	5 (7.6%)
Investigations	10 (31.3%)	12 (35.3%)	22 (33.3%)
Alanine aminotransferase increased	6 (18.8%)	5 (14.7%)	11 (16.7%)
Aspartate aminotransferase increased	3 (9.4%)	4 (11.8%)	7 (10.6%)
Blood creatinine increased	4 (12.5%)	5 (14.7%)	9 (13.6%)
Blood glucose increased	2 (6.3%)	0	2 (3.0%)
Metabolism and nutrition disorders	21 (65.6%)	20 (58.8%)	41 (62.1%)
Decreased appetite	2 (6.3%)	0	2 (3.0%)
Diabetes mellitus	3 (9.4%)	3 (8.8%)	6 (9.1%)
Hypercholesterolaemia	4 (12.5%)	2 (5.9%)	6 (9.1%)
Hyperkalaemia	8 (25.0%)	5 (14.7%)	13 (19.7%)
Hyperlipidaemia	5 (15.6%)	7 (20.6%)	12 (18.2%)
Hypertriglyceridaemia	0	2 (5.9%)	2 (3.0%)
Hyperuricaemia	0	3 (8.8%)	3 (4.5%)
Hypomagnesaemia	5 (15.6%)	3 (8.8%)	8 (12.1%)
Hypophosphataemia	2 (6.3%)	2 (5.9%)	4 (6.1%)
Nervous system disorders	3 (9.4%)	6 (17.6%)	9 (13.6%)
Headache	2 (6.3%)	4 (11.8%)	6 (9.1%)
Hypoaesthesia	0	2 (5.9%)	2 (3.0%)
Psychiatric disorders	7 (21.9%)	5 (14.7%)	12 (18.2%)
Insomnia	7 (21.9%)	5 (14.7%)	12 (18.2%)
Renal and urinary disorders	2 (6.3%)	5 (14.7%)	7 (10.6%)
Dysuria	2 (6.3%)	2 (5.9%)	4 (6.1%)
Respiratory, thoracic and mediastinal disorders	5 (15.6%)	8 (23.5%)	13 (19.7%)
Cough	4 (12.5%)	5 (14.7%)	9 (13.6%)
Rhinorrhoea	1 (3.1%)	2 (5.9%)	3 (4.5%)
Skin and subcutaneous tissue disorders	10 (31.3%)	10 (29.4%)	20 (30.3%)
Acne	4 (12.5%)	5 (14.7%)	9 (13.6%)
Alopecia	6 (18.8%)	4 (11.8%)	10 (15.2%)
Pruritus	2 (6.3%)	0	2 (3.0%)
Vascular disorders	5 (15.6%)	6 (17.6%)	11 (16.7%)
Haematoma	2 (6.3%)	0	2 (3.0%)
Hypertension	2 (6.3%)	3 (8.8%)	5 (7.6%)

Number of patients and percentage of patients (%) are shown.

Sorting order: alphabetical by SOC and preferred term.

The events, both in the initial phase and postrandomization period, are presented.

N: number of patients in each arm.

Source: Table 12.6.1.4.1.1

Table 7 Serious TEAEs by SOC and Preferred Term (MedDRA Vesion 16.1) (SAF)

MedDRA (v16.1) System Organ Class Preferred Term	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Overall	11 (34.4%)	13 (38.2%)	24 (36.4%)
Eye disorders	1 (3.1%)	0	1 (1.5%)
Diabetic retinopathy	1 (3.1%)	0	1 (1.5%)

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MedDRA (v16.1) System Organ Class Preferred Term	Optimized Dose Arm (N = 32)	Standard Dose Arm (N = 34)	Total (N = 66)
Gastrointestinal disorders	1 (3.1%)	2 (5.9%)	3 (4.5%)
Diarrhoea	0	1 (2.9%)	1 (1.5%)
Dyspepsia	0	1 (2.9%)	1 (1.5%)
Enteritis	1 (3.1%)	0	1 (1.5%)
Immune system disorders	2 (6.3%)	3 (8.8%)	5 (7.6%)
Transplant rejection	2 (6.3%)	3 (8.8%)	5 (7.6%)
Infections and infestations	4 (12.5%)	5 (14.7%)	9 (13.6%)
Cytomegalovirus gastritis	0	1 (2.9%)	1 (1.5%)
Cytomegalovirus infection	0	1 (2.9%)	1 (1.5%)
Meningitis aseptic	1 (3.1%)	0	1 (1.5%)
Pneumonia	0	1 (2.9%)	1 (1.5%)
Polyomavirus-associated nephropathy	1 (3.1%)	1 (2.9%)	2 (3.0%)
Pulmonary tuberculosis	1 (3.1%)	0	1 (1.5%)
Urinary tract infection	1 (3.1%)	1 (2.9%)	2 (3.0%)
Varicella	1 (3.1%)	0	1 (1.5%)
Injury, poisoning and procedural complications	0	1 (2.9%)	1 (1.5%)
Post procedural haematoma	0	1 (2.9%)	1 (1.5%)
Investigations	3 (9.4%)	5 (14.7%)	8 (12.1%)
Blood creatinine increased	2 (6.3%)	4 (11.8%)	6 (9.1%)
Blood glucose increased	1 (3.1%)	0	1 (1.5%)
Cytomegalovirus test positive	0	1 (2.9%)	1 (1.5%)
Renal and urinary disorders	1 (3.1%)	2 (5.9%)	3 (4.5%)
Dysuria	1 (3.1%)	0	1 (1.5%)
Haematuria	0	1 (2.9%)	1 (1.5%)
Renal injury	0	1 (2.9%)	1 (1.5%)
Vascular disorders	1 (3.1%)	0	1 (1.5%)
Femoral artery occlusion	1 (3.1%)	0	1 (1.5%)

Number of patients and percentage of patients (%) are shown.
The events, both in the initial phase and postrandomization period, are presented.
Sorting order: alphabetical by SOC and preferred term.
N: Number of patients in each arm.
Source: Table 12.6.1.7.1

CONCLUSIONS:

No significant differences were found in the primary variable of this study between treatment arms. There were no substantial differences between treatment arms in efficacy or safety.

This pilot and exploratory study revealed the optimized dose of Advagraf had a clinically acceptable safety profile, and was generally as well tolerated and effective as the standard dose of tacrolimus for Asian patients who were randomized after the 4 weeks of initial phase when the target tacrolimus trough level was decreased gradually. However, as this study was a 52-week open-label, pilot and exploratory study with approximately 70 patients, these findings have to be confirmed in a long-term double-blind study with more patients.

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