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

SYNOPSIS

Title of Study: A Multicenter, Randomized, Comparison, Open-label, Phase IV Study to Assess the Efficacy and Safety of Advagraf® Switching From Cyclosporine Between the Group That Was Treated With a 50% Reduced Corticosteroid and the Group With Maintained Corticosteroid for Stable Kidney Transplant Recipients

Investigators/Coordinating Investigator:

Principal Investigator

Name of Sponsor/Company: Astellas Pharma Korea, Inc.		
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Name of Active Ingredient: Tacrolimus		

Study Center(s): Total 19 centers

[redacted]

Publication Based on the Study: Not yet (Q4 2016)

Study Period: From 21 Nov 2013 (FPI) to 07 Nov 2015 (LPO)

Study Initiation Date (Date of First Enrollment): 21 Nov 2013

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Study Completion Date (Date of Last Evaluation): 07 Nov 2015

Phase of Development: Phase IV

Objectives:

The primary objective is to explore change in the eGFR from baseline to Week 24 in stable kidney transplant recipients after switching from Cyclosporine + corticosteroid immunosuppressive regimen to Advagraf® + corticosteroid immunosuppressive regimen, between the group that was treated with gradually reduced corticosteroid by 50% from Weeks 4 to 12, and the group with maintained corticosteroid.

The secondary objectives are to assess creatinine clearance and incidence of acute rejection in groups with Advagraf®+50% reduced corticosteroid and with Advagraf®+maintained corticosteroid, and assess patient's satisfaction and safety of Advagraf®-based immunosuppressive regimen.

Methodology:

This was a multicenter, exploratory, randomized, comparison, open-labeled, Phase IV study.

Only in subjects who provided written consent for the study participation at screening visit, protocol-specified examinations and tests were conducted. Subjects determined eligible were randomized to either Group 1 or Group 2, and received 24-week Advagraf®-based immunosuppressive regimen. Group 1 reduced corticosteroid slowly until 50% lower dose from Week 4 to Week 12 in 24-week Advagraf treatment, while Group 2 received the same corticosteroid dose for 24-week treatment period. However, the type of corticosteroid remained unchanged from existing one. The recommended initial dose of Advagraf® was 0.05 - 0.07 mg/kg/day.

- ☐ Group 1 (Advagraf + 50% reduced corticosteroid)
- ☐ Group 2 (Advagraf + maintained corticosteroid dose)

1) Efficacy assessment

a. Renal Function

eGFR was determined using MDRD equation at Screening visit (Visit 1), Visit 5, and the End of Study visit (Visit 6). Also, creatinine clearance was determined using Cockcroft-Gault equation.

MDRD (IDMS (isotope dilution mass spectrometer)) equation is as below:

$eGFR\ (mL/min/1.73m^2) = 175 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742$ (if females)

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Cockcroft-Gault equation is as below:

Creatinine clearance (ml/min) = {[(140 - age) × weight] / 72 × S_{cr}} × 0.85 (in female)

*age: years, weight: kilograms, Scr (serum creatinine): mg/dL

b. Acute Rejection Episodes

Acute rejection was evaluated after the investigational drug administered.

When following test results were found, acute rejection was suspected.

- Serum creatinine level increases at least 30% higher than baseline or over 0.3 mg/dL in 2 consecutive measurements, and
- Kidney nuclear medicine test or ultrasound test indicates suspected rejection

When the symptoms above were observed, it was confirmed by biopsy and evaluated by a local pathologist using following: “Banff 07 Classification of Renal Allograft Pathology: Updates and Future Directions”

c. Satisfaction of Medication

Treatment satisfaction of Advagraf-based immunosuppressive regimen was evaluated at the end of treatment of investigational drug (Visit 6) by using questionnaire.

2) Safety Assessment

a. Vital Signs

Treatment satisfaction of Advagraf-based immunosuppressive regimen was evaluated at the end of treatment of investigational drug (Visit 6) by using questionnaire

b. Adverse Events

Adverse events (AEs) were continuously collected from the time of signing informed consent forms until the last visit.

Any symptoms or sings before the first investigational drug dose were recorded as baseline. AEs were recorded from the date of the first study drug dose until the end of study/early termination. Any AE worsening during the study was allowed to be recorded as AEs. AEs that started after a subject completed the study were not collected.

Ongoing AEs at the last visit were followed up as necessary to evaluate subjects’ safety properly. If the AE was resolved during the study, the end date was recorded in CRFs.

c. Laboratory Assessments

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Routine laboratory tests were conducted in all scheduled visits at the local laboratory. At screening, recent test results within 2 weeks were allowed to be used. Blood samples were collected after at least 6-hour fasting, and before investigational drug dose in the morning. Samples were analyzed in the local laboratory.

d. Pregnancy Test

For females with child-bearing potential, urine or serum pregnancy test (β-HCG) was conducted at Visit 1 and EOS visit (Visit 6).

e. Physical Examination

Physical examination was conducted at Screening visit (Visit 2) and EOS visit (Visit 6).

Before starting the treatment, presence of Cyclosporine-related side effects in appearance, especially hypertrichosis and gingival hyperplasia, were confirmed, and for subjects with the symptoms, the severity was additionally evaluated. At EOS visit (Visit 6), re-evaluation was conducted only for subjects with symptoms at Screening visit (Visit 2) who were evaluated for severity. Severity was evaluated by investigators using 5-point scale (minimal, mild, moderate, severe, and extreme). However, in subjects without symptom at Screening visit (Visit 2), events that occurred after enrollment were considered as AEs.

Number of Patients (Planned, Enrolled and Analyzed):

This is an exploratory study and the sample size was not determined based on statistical consideration. This study aimed to enroll appropriately total 150 subjects: 75 subjects in Group 1 (Advagraf + 50% reduced corticosteroid) and 75 subjects in Group 2 (Advagraf + maintained corticosteroid dose).

Among 153 subjects screened, 150 subjects were enrolled, except 3 screening failures: 73 subjects were randomized into Advagraf + 50% reduced corticosteroid (hereinafter ‘Group 1’) and 77 subjects were randomized into Advagraf + maintained corticosteroid dose (hereinafter ‘Group 2’). In the course of the study, 28 subjects were withdrawn. Except the withdrawn subjects, total 122 subjects completed the study.

Among subjects who provided written consent for the study participation, 150 subjects were randomized. Among them, 149 subjects were included in the Safety Set. Among 149 subjects in the Safety Set, 149 subjects were included in the full analysis set (FAS). Among FAS, 94 subjects completed the study as per the protocol were included in the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1) At least 20 years of age

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2) Patients who had a kidney transplant at least 12 months before enrollment (including a kidney re-transplantation)
3) Patients who underwent Cyclosporine-based immunosuppressive regimen after the kidney transplantation and whose Cyclosporine dose remained unchanged for 4 weeks before enrollment
4) The immunosuppressive regimen (combination therapy) remained unchanged for at least 4 weeks before enrollment
5) Patients receiving corticosteroid for immunosuppressive therapy
6) eGFR ≥ 30 ml/min
7) Females of child-bearing potential who had negative serum pregnancy test at enrollment, and agreed with using effective contraception during the study
8) Patients who have received full explanation and understood about the study purpose and risks, and provided written consent
9) Clinically stable in the investigator's opinion

Exclusion Criteria

1) Patients who had received an organ transplant other than a kidney
2) Patients who had an acute rejection episode within 12 weeks before enrollment, or had an acute rejection episode requiring anti-lymphocyte antibody therapy within 24 weeks before enrollment
3) Patients who had been diagnosed with new-onset malignancy after transplantation, except for basal cell or squamous cell carcinoma of the skin that had been successfully treated
4) Patients who received a kidney transplant from full-HLA identical donor
5) Patients known to have focal segmental glomerulosclerosis (FSGS) or membranoproliferative glomerulonephritis type II (MPGN Type II) as an underlying disease
6) Patients who had elevated SGPT/ALT and/or SGOT/AST and/or total bilirubine levels ≥ 2 times the upper limit of normal (ULN)
7) Patients with cirrhosis
8) Pregnant or breast-feeding women
9) Known allergy or resistance to ingredients of Tacrolimus, macrolide antibiotics, corticosteroid, co-administered immunosuppressive agents, or the study drug

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10) Unstable medical conditions that may affect the study objectives in the investigator's opinion

11) Patients who had received any prohibited treatment within 28 days before enrollment, or was on any prohibited treatment

12) Patients who was participating in other clinical study, or had received any investigational drug within 28 days before enrollment

13) Any types of substance abuse, mental illness, or other conditions that may interfere with communication with the investigator, in the investigator's opinion

14) Patients who were unable to follow scheduled visits and treatment compliance as stated in the protocol

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

Investigational product

ADVAGRAF® 0.5, 1, 5mg (Tacrolimus)

Dose/Administration

Trough level of 5 - 15 ng/ml was recommended for the first 4 weeks by monitoring trough level of Tacrolimus after switching to Advagraf® at the recommended initial dose. Later the dose was reduced to maintain trough level of 3 - 10 ng/ml until the end of the study.

Lot Numbers

ADVAGRAF® 0.5mg: [redacted]

ADVAGRAF® 1mg: [redacted]

ADVAGRAF® 5mg: [redacted]

Duration of Treatment (or Duration of Study, if applicable): 24 Weeks

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

Criteria for Evaluation:

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Primary endpoint

Change in the eGFR from before the treatment (baseline) to that at Week 24

Secondary endpoints

1) Change in the eGFR from before the treatment (baseline) to that at Week 12
2) Change in the creatinine clearance from before the treatment (baseline) to those at Weeks 12 and 24
3) Incidence of acute rejection and time to onset of acute rejection
4) Treatment satisfaction of Advagraf®-based immunosuppressive regimen

Safety

1) Adverse Events
2) Physical examination (including cyclosporine related cosmetic side effect)
3) Laboratory tests
4) Vital sign measurements.

Statistical Methods:

Primary endpoint

Change in the eGFR from before the treatment (baseline, Visit 2) to that at Week 24 (Visit 6) in each group was analyzed using paired t-test, and difference between the groups in eGFR before the treatment (baseline, Visit 2), at Week 24 (Visit 6), and change from before the treatment (baseline, Visit 2) to that at Week 24 was analyzed using t-test.

Secondary endpoints

1) Change in the eGFR before the treatment (baseline) to that on Week 12

Change in the eGFR before the treatment (baseline, Visit 2) to that on Week 12 (Visit 5) in each group was analyzed using paired t-test, and difference between the groups in eGFR before the treatment (baseline, Visit 2), on Week 12 (Visit 5), and change before the treatment (baseline, Visit 2) to that on Week 12 was analyzed using t-test.

2) Change in the creatinine clearance before the treatment (baseline) to those on Weeks 12 and 24

Change in the creatinine clearance before the treatment (baseline, Visit 2) to that on Week 12 (Visit 5) and Week 24 (Visit 6) in each group was analyzed using paired t-test, and difference between the groups in change of the creatinine clearance before the treatment (baseline, Visit 2) to those on Weeks 12 and 24 was analyzed using t-test.

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3) Incidence of acute rejection and time of onset

Frequency and percentage of subjects who showed the first acute rejection during the study, as well as their 95% CI were to be provided. Here, difference between the groups was to be analyzed using Chi-square test or Fisher's Exact test.

For the time from the first study drug administration (Visit 2) to the first acute rejection onset date (applicable visit date), Kaplan-Meier estimation was to be used to produce Kaplan-Meier curve. And for the time to the first acute rejection onset, the median and 95% CI were to be provided for each group, and log-rank test was to be used to analyze difference between the groups.

However, statistical analysis for incidence of acute rejection and time of onset was not conducted, because no subject showed acute rejection during the study.

4) Treatment satisfaction of Advagraf®-based immunosuppressive regimen

Frequency and percentage of each item contained in the treatment satisfaction survey of Advagraf-based immunosuppressive regimen at Week 24 (Visit 6) were provided, and Chi-square test or Fisher's Exact test was used to test difference in individual items of treatment satisfaction between the groups.

Safety

1) Adverse Events

Frequency of AEs by group and the number and percentage of subjects with AEs were provided. The details are as below:

① Proportion of subjects with AEs and frequency of AEs by group were calculated, and 95% CI for incidences of adverse events (AEs), adverse drug reactions (ADRs)†, serious adverse events (SAEs), and withdrawal due to AEs‡ was estimated. Chi-square test or Fisher's Exact test was used to determine difference in the incidences between the groups.

② The number of subjects experiencing AEs, ADRs†, and SAEs and the number of events were calculated by group, and the incidence was estimated.

③ For AEs occurred in each group, the number and percentage of events were calculated by severity, outcomes, actions taken, relationship, and use of corrective treatment.

④ The type of AEs occurred in each group was categorized based on severity and relationship, and the number and percentage of each event were calculated.

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2) Physical examination

Shift from normal to abnormal findings in physical examination at Week 24 (Visit 6) compared to baseline (Visit 2) was summarized with the frequency and percentage, and Chi-square test or Fisher's Exact test was used to analyze difference between the groups. In addition, a list of subjects with abnormal findings was provided.

3) Hypertrichosis/Gingival hyperplasia

In subjects who had hypertrichosis and gingival hyperplasia before the investigational drug treatment (baseline, Visit 2), frequency and percentage of the severity of hypertrichosis and gingival hyperplasia at Week 24 (Visit 6) compared to baseline (Visit 2) were planned to be provided. However, due to very small number of subjects with hypertrichosis/gingival hyperplasia during the study period, a list of subject was provided, instead of analyzing the frequency and percentage.

4) Vital signs

Vital sign measurements at each visit were provided, and t-test was used to compare difference between the groups. In addition, paired t-test was used to determine intra-group changes at Week 24 (Visit 6) from baseline (Visit 2), while t-test was used to analyze difference in changes between the groups.

5) Laboratory test

Laboratory test results at each visit were provided, and t-test was used to analyze difference between the groups. In addition, paired t-test was used to determine intra-group changes at Week 24 (Visit 6) from baseline (Visit 2), while t-test was used to analyze difference in changes between the groups.

In addition, shift from normal (Normal, NCS) to abnormal (CS) findings in laboratory tests at Week 24 (Visit 6) compared to baseline (Visit 2) was summarized with the frequency and percentage, and Chi-square test or Fisher's Exact test was used to analyze difference between the groups. In addition, a list of subjects showing clinically significant abnormality (CS) was provided.

Summary of Results/Conclusions:

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Primary Efficacy Endpoint:

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In FAS, when analyzing change in the eGFR from before the treatment (baseline, Visit 2) to that at Week 24 (Visit 6), Group 1 showed mean increase of 1.53±9.07, and the intra-group change was not statistically significant (p=0.1567). Group 2 showed mean increase of 3.39±10.63, and the intra-group change was statistically significant (p=0.0065). The difference in change in the eGFR from baseline to Week 24 between the groups was not statistically significant (p=0.2538) (Table 4)

Secondary Efficacy Endpoints:

1) Change in the eGFR from before the treatment (baseline) to that at Week 12 (FAS)

In FAS, when analyzing change in the eGFR before the treatment (baseline, Visit 2) to that on Week 12 (Visit 5), Group 1 showed mean increase of 1.21±7.19, and the intra-group change was not statistically significant (p=0.1582). Group 2 showed mean increase of 3.75±13.41, and the intra-group change was statistically significant (p=0.0164). The difference in change in the eGFR from baseline to Week 12 between the groups was not statistically significant (p=0.1480) (Table 5)

2) Change in creatinine clearance from before the treatment (baseline) to those at Weeks 12 and 24

In FAS, when analyzing change in the creatinine clearance before the treatment (baseline, Visit 2) to that on Week 12 (Visit 5), Group 1 showed mean increase of 0.68±7.03, and the intra-group change was not statistically significant (p=0.4129). Group 2 showed mean increase of 1.51±8.39, and the intra-group change was not statistically significant (p=0.1212). The difference between the groups in change of the creatinine clearance from baseline to Week 12 was not statistically significant (p=0.5182) (Table 6)

In FAS, when analyzing change in the creatinine clearance before the treatment (baseline, Visit 2) to that on Week 24 (Visit 6), Group 1 showed mean increase of 0.93±8.44, and the intra-group change was not statistically significant (p=0.3520). Group 2 showed mean increase of 1.77±8.22, and the intra-group change was not statistically significant (p=0.0623). The difference between the groups in change of the creatinine clearance from baseline to Week 24 was not statistically significant (p=0.5389) (Table 6)

3) Incidence of Acute Rejection and Time of Onset

No subject experienced at least one acute rejection during the study.

4) Treatment satisfaction of Advagraf-based immunosuppressive regimen

In FAS, when evaluating treatment satisfaction of Advagraf-based immunosuppressive regimen at Week 24 (Visit 6) after the initiation of investigational drug treatment, answer to Q1 (Is it more convenient for you to take your drug after switching to once-daily Advagraf?) was ‘Definitely Yes’ in 39.44% (28/71 subjects), ‘Yes’ in 30.99% (22/71 subjects), and ‘Average’ in 16.90% (12/71 subjects) in Group 1, while it was ‘Definitely Yes’ in 33.78% (25/74 subjects), ‘Yes’ in 48.65% (36/74 subjects), and ‘Average’ in 9.46% (7/74 subjects) in Group 2. The difference between the groups was not statistically significant (p=0.2444). (Table 7)

Answer to Q2 (Is the number of missed dose decreased after switching to Advagraf?) was ‘Definitely Yes’ in 19.72% (14/71 subjects), ‘Yes’ in 23.94% (17/71 subjects), ‘Average’ in 15.49% (11/71 subjects), ‘No’ 19.72% (14/71 subjects), and ‘Definitely No’ in 21.13% (15/71 subjects) in Group 1, while it was ‘Definitely Yes’ in 16.22% (12/74 subjects), ‘Yes’ in 31.08% (23/74 subjects), ‘Average' in 16.22% (12/74 subjects), ‘No’ in 21.62%

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(16/74 subjects), and 'Definitely No' in 14.86% (11/74 subjects) in Group 2. The difference between the groups was not statistically significant (p=0.7753). (Table 7)

Answer to Q3 (Have you ever missed or discontinued Cyclosporine dose due to inconvenience of twice-daily dosing before participating in the study?) was 'Definitely No' in 33.80% (24/71 subjects), 'No' in 28.17% (20/71 subjects), 'Average' in 11.27% (8/71 subjects), 'Yes' in 21.13% (15/71 subjects), and 'Definitely Yes' in 5.63% (4/71 subjects) in Group 1, while it was 'Definitely No' in 38.36% (28/73 subjects), 'No' in 32.88% (24/73 subjects), 'Average' in 6.85% (5/73 subjects), 'Yes' in 19.18% (14/73 subjects), and 'Definitely Yes 2.74% (2/73 subjects) in Group 2. The difference between the groups was not statistically significant (p=0.7289). (Table 7)

Answer to Q4 (When you missed Cyclosporine dose, was it usually in the morning or evening?) was 'Never missed dose' in 43.66% (31/71 subjects) and 'Morning' and 'Evening' each in 28.17% (20/71 subjects) in Group 1, while it was 'Never missed dose' in 60.27% (44/73 subjects), 'Evening' in 32.88% (24/73 subjects), and 'Morning' in 6.85% (5/73 subjects) in Group 2. The difference between the groups was statistically significant (p=0.0030). (Table 7)

Answer to Q5 (Before participating in the study, what would be the biggest reason of missed Cyclosporine dose at the scheduled time?) was 'Difficult to take the drug at the scheduled time due to life style and social life' in 65.45% (36/55 subjects), 'Side effects from immunosuppressive agents' in 5.45% (3/55 subjects), 'Lack of understanding in dosing or forget dosing' in 25.45% (14/55 subjects), 'Physical and emotional burden due to long-term use of immunosuppressive' in 1.82% (1/55 subjects) and 'Social taboo or prejudice on taking immunosuppressive agents' in 1.82% (1/55 subjects) in Group 1, while it was 'Difficult to take the drug at the scheduled time due to life style and social life' in 65.38% (34/52 subjects), 'Side effects from immunosuppressive agents' in 3.85% (2/52 subjects), 'Lack of understanding in dosing or forget dosing' in 26.92% (14/52 subjects), 'Physical and emotional burden due to long-term use of immunosuppressive agents' in 3.85% (2/52 subjects), and 'Social taboo or prejudice on taking immunosuppressive agents' was 0% in Group 2. The difference between the groups was not statistically significant (p=0.9887) (Table 7)

Safety Results:

Incidence of AEs that occurred after the investigational drug treatment, regardless of relationship to the investigational drug, was 58.33% (42/72 subjects, 98 events) in Group 1 and 64.94% (50/77 subjects, 109 events) in Group 2. The difference in incidence of AEs between the groups was not statistically significant (p=0.4073).(Table 8)

Among them, incidence of ADRs that were 'probably related' or 'possibly related' to the investigational drug was 15.28% (11/72 subjects, 17 events) in Group 1 and 12.99% (10/77 subjects, 15 events) in Group 2. The difference in incidence of ADRs between the groups was not statistically significant (p=0.6880). (Table 8)

Incidence of SAEs was 8.33% (6/72 subjects, 6 events) in Group 1 and 10.39% (8/77 subjects, 11 events) in Group 2. The difference in incidence of SAEs between the groups was not statistically significant (p=0.6673). (Table 9)

Incidence of withdrawal due to AEs was 2.78% (2/72 subjects, 3 events) in Group 1 and 3.90% (3/77 subjects, 4 events) in Group 2. The difference in incidence of withdrawal due to AEs between the groups was not statistically significant (p=1.0000). (Table 8)

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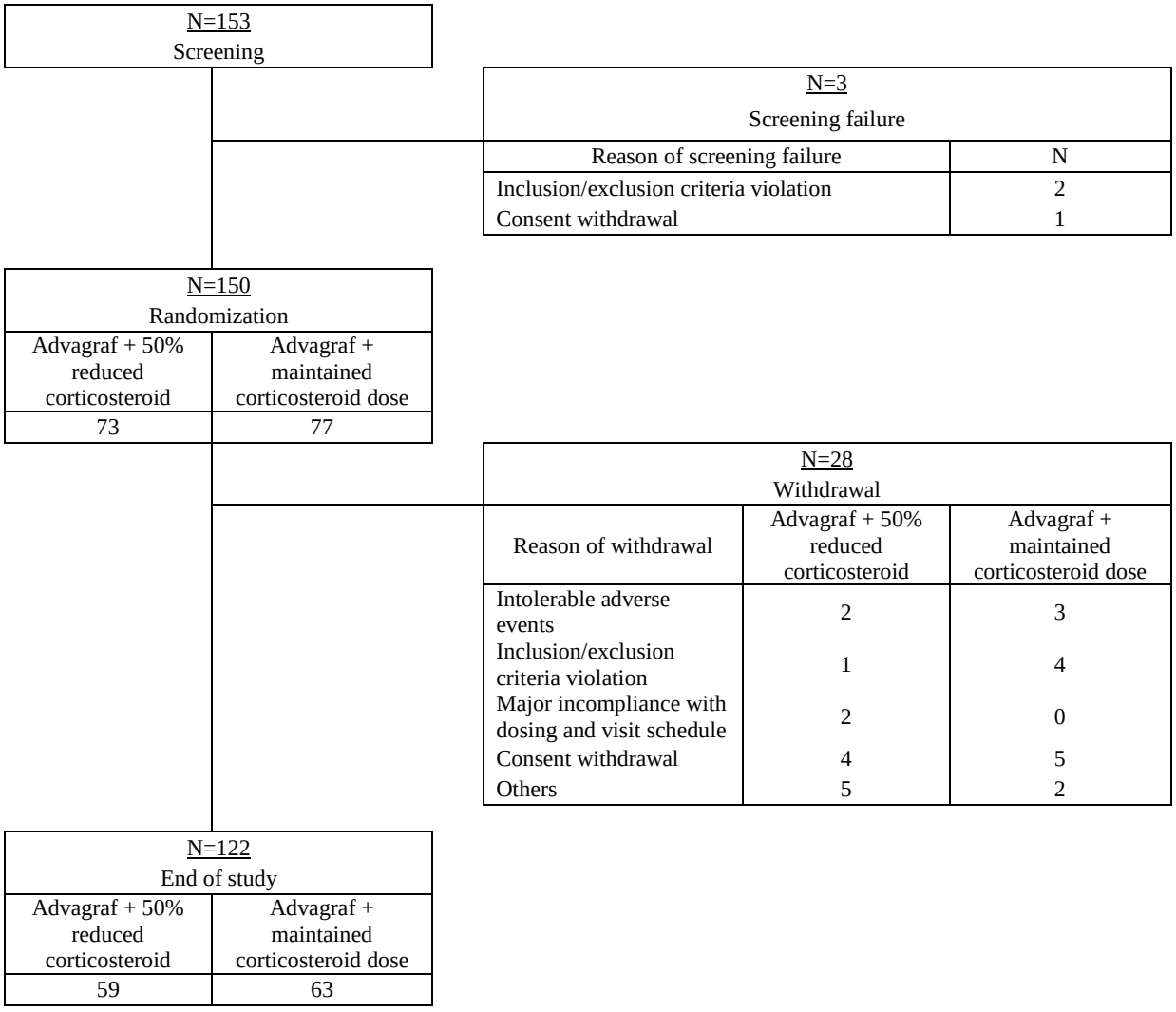
CONCLUSIONS:

In conclusion, after switching to Advagraf-based immunosuppressive regimen from Cyclosporine in the groups with a 50% reduced corticosteroid and with maintained corticosteroid dose for stable kidney transplant recipients, there was no clinically significant change in terms of renal functions and safety, and the treatment satisfaction increased by virtue of the once daily dosing. In addition, there was no significant difference found in efficacy, treatment satisfaction and safety when comparing the group with a 50% reduced corticosteroid and with maintained corticosteroid dose. It is well known that long-term use of high dose corticosteroid is associated with various side effects. Therefore, based on the study outcomes, 50% reduction of corticosteroid is considered clinically beneficial for kidney transplant recipients after switching to Advagraf-based immunosuppressive regimen from Cyclosporine.

Date of Report: 07 Oct 2016

Figure 1 Disposition of Subjects



Source: CSR Fig 6.1-1 Disposition of Subjects

Table 1 Patient Disposition

	Advagraf+ 50% reduced corticosteroid n (%)	Advagraf+maintained corticosteroid dose n (%)	Total n (%)
Randomization	73 (48.67)	77 (51.33)	150
No investigational drug taken	1 (1.37)	0 (0.00)	1 (0.67)
Safety Set[1)]	72 (48.32)	77 (51.68)	149 (99.33)
FAS[2)]	72 (48.32)	77 (51.68)	149 (99.33)
Intolerable adverse events	2 (2.78)	3 (3.90)	5 (3.36)
Inclusion/exclusion criteria violation	1 (1.39)	5 (6.49)	6 (4.03)
Major incompliance with dosing and visit schedule	2 (2.78)	0 (0.00)	2 (1.34)
Consent withdrawal	3 (4.17)	5 (6.49)	8 (5.37)
Others (violation of corticosteroid dosing schedule)	4 (5.56)	0 (0.00)	4 (2.68)
Others (withdrawal from the study due to underlying disease of MPGN (unknown type))	1 (1.39)	0 (0.00)	1 (0.67)
Others (difficult to continue the study in the investigator's opinion)	0 (0.00)	2 (2.60)	2 (1.34)
Violation of concomitant immunosuppressive agent dose	8 (11.11)	9 (11.69)	17 (11.41)
Missed Visit 6 efficacy evaluation	1 (1.39)	0 (0.00)	1 (0.67)
Prescription of drugs available in the market	1 (1.39)	1 (1.30)	2 (1.34)
Prescription of investigational drug before laboratory test at screening	4 (5.56)	3 (3.90)	7 (4.70)
PPS[3)]	45 (47.87)	49 (52.13)	94 (62.67)

1) Randomized subjects who do not fall into the exclusion criteria of the Safety Set

2) Subjects in the Safety Set who do not fall into FAS exclusion criteria

3) Subjects in FAS who do not fall into PPS exclusion criteria

Source: CSR Table 6.1-1 Protocol Deviations and Subject Disposition in Analysis Population

Table 2 Demographic Characteristics

		Advagraf + 50% reduced corticosteroid (N=72)	Advagraf + maintained corticosteroid dose (N=77)	Total (N=149)	p-value
		n (%)	n (%)	n (%)	
Sex	Male	48 (66.67)	45 (58.44)	93 (62.42)	0.3003
	Female	24 (33.33)	32 (41.56)	56 (37.58)	Chi-square test
Age	mean±std (old)	49.89 ± 10.13	53.97 ± 9.98	52.00 ± 10.23	0.0143
	median	50.00	53.00	52.00	t-test
	min~max	31.00 ~ 73.00	34.00 ~ 77.00	31.00 ~ 77.00	
	30 - 39 years	15 (20.83)	4 (5.19)	19 (12.75)	
	40 - 49 years	18 (25.00)	23 (29.87)	41 (27.52)	
	50 - 59 years	26 (36.11)	25 (32.47)	51 (34.23)	
	60 years or over	13 (18.06)	25 (32.47)	38 (25.50)	
Height	mean±std (cm)	166.60 ± 8.36	164.23 ± 7.96	165.37 ± 8.21	0.0788

		Advagraf + 50% reduced corticosteroid (N=72)	Advagraf + maintained corticosteroid dose (N=77)	Total (N=149)	p-value
		n (%)	n (%)	n (%)	
	median	168.20	163.00	165.70	t-test
	min~max	145.00 ~ 182.00	151.00 ~ 183.50	145.00 ~ 183.50	
Weight	mean±std (kg)	65.18 ± 10.53	63.53 ± 11.55	64.33 ± 11.06	0.3632
	median	64.55	62.00	63.00	t-test
	min~max	44.00 ~ 92.70	42.00 ~ 98.00	42.00 ~ 98.00	
BMI	mean±std (kg/m^2)	23.43 ± 2.91	23.43 ± 3.00	23.43 ± 2.95	0.9968
	median	23.77	23.27	23.52	t-test
	min~max	16.60 ~ 29.87	16.00 ~ 31.64	16.00 ~ 31.64	
	Underweight (< 18.5 kg/m^2)	4 (5.56)	4 (5.19)	8 (5.37)	
	Normal weight (18.5 kg/m^2 ~ < 23.0 kg/m^2)	25 (34.72)	33 (42.86)	58 (38.93)	
	Overweight (23.0 kg/m^2 ~ < 25.0 kg/m^2)	21 (29.17)	18 (23.38)	39 (26.17)	
	Obesity (≥ 25.0 kg/m^2)	22 (30.56)	22 (28.57)	44 (29.53)	

Weight: Visit 2

BMI: Weight (kg) / Height (m)^2

Source: CSR Table 6.3.1-1 Baseline Information (Subjects)

Table 3 Trough level of Tacrolimus

Time Point	Advagraf + 50% reduced corticosteroid (N=72)						Advagraf + maintained corticosteroid dose (N=77)					
	n	mean	± std	median	min	~ max	n	mean	± std	median	min	~ max
Visit 3(Week 1)	68	5.60	± 3.60	4.65	1.70	~ 22.30	73	5.08	± 3.02	4.30	1.20	~ 14.20
Visit 4(Week 4)	66	5.65	± 2.70	5.30	1.80	~ 18.90	68	5.14	± 2.21	4.70	2.00	~ 14.30
Visit 5(Week 12)	65	5.18	± 1.59	4.90	2.30	~ 9.10	65	4.96	± 1.86	4.50	2.20	~ 11.70
Visit 6(Week 24)	56	5.19	± 1.89	5.05	2.20	~ 12.20	62	5.01	± 1.69	5.00	1.80	~ 9.40

Source: CSR Table 7-2 Trough blood level of Tacrolimus

Table 4 Change in the eGFR from before the treatment (baseline) to that at Week 24 (FAS)

Time Point	Advagraf + 50% reduced corticosteroid (N=72)						Advagraf + maintained corticosteroid dose (N=77)						p-value* t-test
	n	mean	± std	median	min	~ max	n	mean	± std	median	min	~ max	
Visit 2(Baseline)	72	61.79	± 17.54	61.50	32.00	~ 108.00	77	62.47	± 14.95	62.00	27.00	~ 95.00	0.7997
Visit 6(Week 24)	58	63.17	± 19.31	62.00	27.00	~ 118.00	63	64.94	± 17.47	65.00	32.00	~ 115.00	0.5988

Visit 6(Week 24)(LOCF)	72	63.32	± 19.15	62.00	27.00	~ 118.00	77	65.86	± 18.26	66.00	32.00	~ 127.00	0.4090
Difference(Visit 6(LOCF) - Visit 2)	72	1.53	± 9.07	1.50	-24.00	~ 34.00	77	3.39	± 10.63	1.00	-16.00	~ 47.00	0.2538
p-value(paired t-test)†		0.1567						0.0065					

* p-value: p-value for difference in eGFR between the group of "Advagraf + 50% reduced corticosteroid" and the group of "Advagraf + maintained corticosteroid dose"

† p-value (paired t-test): p-value for intra-group change

Source: CSR Table 8.1.1.1-1 Change in the eGFR before the treatment (baseline) to that on Week 24 (FAS)

Table 5 Change in the eGFR from before the treatment (baseline) to that at Week 12 (FAS)

Time Point	Advagraf + 50% reduced corticosteroid (N=72)						Advagraf + maintained corticosteroid dose (N=77)						p-value* t-test
	n	mean	± std	median	min	~ max	n	mean	± std	median	min	~ max	
Visit 2(Baseline)	72	61.79	± 17.54	61.50	32.00	~ 108.00	77	62.47	± 14.95	62.00	27.00	~ 95.00	0.8001
Visit 5(Week 12)	66	63.17	± 17.93	63.50	31.00	~ 107.00	66	65.18	± 19.25	64.00	34.00	~ 134.00	0.5349
Visit 5(Week 12)(LOCF)	72	63.00	± 18.33	61.00	31.00	~ 108.00	77	66.22	± 19.84	65.00	33.00	~ 134.00	0.3060
Difference(Visit 5(LOCF) - Visit 2)	72	1.21	± 7.19	0.00	-20.00	~ 15.00	77	3.75	± 13.41	1.00	-25.00	~ 89.00	0.1480
p-value(paired t-test)†		0.1582						0.0164					

* p-value: p-value for difference in eGFR between the group of "Advagraf + 50% reduced corticosteroid" and the group of "Advagraf + maintained corticosteroid dose"

† p-value (paired t-test): p-value for intra-group change

Source: CSR Table 8.1.1.2-1 Change in the eGFR before the treatment (baseline) to that on Week 12 (FAS)

Table 6 Change in creatinine clearance from before the treatment (baseline) to those at Weeks 12 and 24 (FAS)

Time Point	Advagraf + 50% reduced corticosteroid (N=72)						Advagraf + maintained corticosteroid dose (N=77)						p-value* t-test
	n	mean	± std	median	min	~ max	n	mean	± std	median	min	~ max	
Visit 2(Baseline)	72	67.46	± 22.71	62.45	29.90	~ 132.90	77	64.22	± 17.60	63.50	26.20	~ 119.80	0.3341
Visit 5(Week 12)	66	68.27	± 22.89	63.00	29.50	~ 130.00	65	64.06	± 17.11	62.80	29.50	~ 100.10	0.2352
Visit 6(Week 24)	58	67.27	± 23.82	62.70	29.00	~ 133.30	62	64.19	± 18.11	63.70	28.90	~ 102.10	0.4300
Visit 5(Week 12)(LOCF)	72	68.14	± 22.84	63.00	29.50	~ 130.00	76	66.09	± 19.24	64.95	29.50	~ 129.20	0.5553
Visit 6(Week 24)(LOCF)	72	68.39	± 23.69	62.75	29.00	~ 133.30	77	65.99	± 19.71	66.00	28.90	~ 129.20	0.5011
Difference(Visit 5(LOCF) - Visit 2)	72	0.68	± 7.03	-0.05	-22.30	~ 16.90	76	1.51	± 8.39	1.00	-24.30	~ 32.60	0.5182
Difference(Visit 6(LOCF) - Visit 2)	72	0.93	± 8.44	0.65	-31.50	~ 24.40	77	1.77	± 8.22	0.80	-22.70	~ 32.60	0.5389
p-value(paired t-test)†		0.4129						0.1212					
p-value(paired t-test)‡		0.3520						0.0623					

* p-value: p-value for difference in creatinine clearance between the group of "Advagraf + 50% reduced corticosteroid" and the group of "Advagraf + maintained corticosteroid dose"

† p-value (paired t-test): p-value for intra-group change from baseline to Week 12 (Visit 5)

‡ p-value (paired t-test): p-value for intra-group change from baseline to Week 24 (Visit 6)

Subject [redacted] (Advagraf + maintained corticosteroid dose)': excluded from the analysis because at Visit 5, creatinine clearance was not calculated due to failure in body weight measurement

Source: 8.1.1.3-1 Change in creatinine clearance before the treatment (baseline) to those on Weeks 12 and 24 (FAS)

Table 7 Treatment satisfaction of Advagraf-based immunosuppressive regimen (FAS)

Question*	Item	Advagraf + 50% reduced corticosteroid (N=72)		Advagraf + maintained corticosteroid dose (N=77)		Total (N=149)		p-value
		n	(%)	n	(%)	n	(%)	
1	Definitely No	3	(4.23)	2	(2.70)	5	(3.45)	0.2444 Exact test
	No	6	(8.45)	4	(5.41)	10	(6.90)	
	Average	12	(16.90)	7	(9.46)	19	(13.10)	
	Yes	22	(30.99)	36	(48.65)	58	(40.00)	
	Definitely Yes	28	(39.44)	25	(33.78)	53	(36.55)	
	Total	71	(48.97)	74	(51.03)	145	(100.00)	
2	Definitely No	15	(21.13)	11	(14.86)	26	(17.93)	0.7753 Chi-square test
	No	14	(19.72)	16	(21.62)	30	(20.69)	
	Average	11	(15.49)	12	(16.22)	23	(15.86)	
	Yes	17	(23.94)	23	(31.08)	40	(27.59)	
	Definitely Yes	14	(19.72)	12	(16.22)	26	(17.93)	
	Total	71	(48.97)	74	(51.03)	145	(100.00)	
3	Definitely No	24	(33.80)	28	(38.36)	52	(36.11)	0.7289 Chi-square test
	No	20	(28.17)	24	(32.88)	44	(30.56)	
	Average	8	(11.27)	5	(6.85)	13	(9.03)	
	Yes	15	(21.13)	14	(19.18)	29	(20.14)	
	Definitely Yes	4	(5.63)	2	(2.74)	6	(4.17)	
	Total	71	(49.31)	73	(50.69)	144	(100.00)	
4	Morning	20	(28.17)	5	(6.85)	25	(17.36)	0.0030 Chi-square test
	Evening	20	(28.17)	24	(32.88)	44	(30.56)	
	Never missed dose	31	(43.66)	44	(60.27)	75	(52.08)	
	Total	71	(49.31)	73	(50.69)	144	(100.00)	
5	Difficult to take the drug at the scheduled time due to life style and social life	36	(65.45)	34	(65.38)	70	(65.42)	0.9887 Exact test
	Side effects from immunosuppressive agents	3	(5.45)	2	(3.85)	5	(4.67)	
	Lack of understanding in dosing or forget dosing	14	(25.45)	14	(26.92)	28	(26.17)	
	Physical and emotional burden due to long-term use of immunosuppressive agents (dependency/addiction, etc.)	1	(1.82)	2	(3.85)	3	(2.80)	
	Social taboo or prejudice on taking immunosuppressive agents	1	(1.82)	0	(0.00)	1	(0.93)	

Question*	Item	Advagraf + 50% reduced corticosteroid (N=72)	Advagraf + maintained corticosteroid dose (N=77)	Total (N=149)	p-value
		n (%)	n (%)	n (%)	
	Total	55 (51.40)	52 (48.60)	107 (100.00)	

* 1. Is it more convenient for you to take your drug after switching to once-daily Advagraf?
2. Is the number of missed dose decreased after switching to Advagraf?
3. Have you ever missed or discontinued Cyclosporine dose due to inconvenience of twice-daily dosing before participating in the study?
4. When you missed Cyclosporine dose, was it usually in the morning or evening?
5. Before participating in the study, what would be the biggest reason of missed Cyclosporine dose at the scheduled time?

Source: CSR Table 8.1.1.5-1 Treatment satisfaction of Advagraf-based immunosuppressive regimen (FAS)

Table 8 Summary of Adverse Events

	Advagraf + 50% reduced corticosteroid (N=72)			Advagraf + maintained corticosteroid dose (N=77)			p-value
	Incidence n (%)	95% CI (Lower limit, upper limit)	Number of events	Incidence n (%)	95% CI (Lower limit, upper limit)	Number of events	
Adverse Events	42 (58.33)	(46.11 , 69.85)	98	50 (64.94)	(53.22 , 75.47)	109	0.4073†
Adverse Drug Reactions[1)]	11 (15.28)	(7.88 , 25.69)	17	10 (12.99)	(6.41 , 22.59)	15	0.6880†
Serious Adverse Events	6 (8.33)	(3.12 , 17.26)	6	8 (10.39)	(4.59 , 19.45)	11	0.6673†
Withdrawal due to AEs[2)]	2 (2.78)	(0.34 , 9.68)	3	3 (3.90)	(0.81 , 10.97)	4	1.0000‡

† Chi-square Test

‡ Fisher's Exact Test

1) Adverse Drug Reactions: "possible related" or "probably related" AEs

2) Withdrawal due to AEs includes "permanent discontinuation" in the actions taken to the study drug and "intolerable AEs" in the reason of withdrawal.

Percentage (%) of incidence was calculated based on the safety population in each group.

95% CI was calculated using Exact Method.

Source: CSR Table 9.1.1-1 Summary of Adverse Events

Table 9 Summary of Serious Adverse Events

Screening No.	Randomization No.	Group	System Organ Class (SOC)	Adverse Event (PT)	Date of onset	Date of disappearance	Severity of AEs	Outcome of AEs	Actions taken to the study drug	Relationship to the study drug	Corrective treatment
[redacted]	[redacted]	Advagraf + 50% reduced corticosteroid	Infections and infestations	Urinary tract infection	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Infections and infestations	Pyelonephritis acute	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Metabolism and nutrition disorders	Hyperglycaemia	[redacted]	[redacted]	Moderate	Recovered	Dose change	Possibly related	Yes
[redacted]	[redacted]	Advagraf + 50% reduced corticosteroid	Nervous system disorders	Headache	[redacted]	[redacted]	Moderate	Recovered	Dose change	Possibly related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Infections and infestations	Arthritis bacterial	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + 50% reduced corticosteroid	Musculoskeletal and connective tissue disorders	Spinal column stenosis	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + 50% reduced corticosteroid	Gastrointestinal disorders	Gastrooesophageal reflux disease	[redacted]	[redacted]	Mild	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Infections and infestations	Gastroenteritis	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Injury, poisoning and procedural complications	Multiple injuries	[redacted]	[redacted]	Severe	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + 50% reduced corticosteroid	Infections and infestations	Urinary tract infection	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Gastrointestinal disorders	Nausea	[redacted]	[redacted]	Moderate	Recovered	Dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Gastrointestinal disorders	Vomiting	[redacted]	[redacted]	Moderate	Recovered	Dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Infections and infestations	Pneumonia	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Eye disorders	Cataract	[redacted]	[redacted]	Mild	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf + maintained corticosteroid dose	Infections and infestations	Pyelonephritis acute	[redacted]	[redacted]	Moderate	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf+ 50% reduced corticosteroid	Infections and infestations	Pyelonephritis acute	[redacted]	[redacted]	Mild	Recovered	No dose change	Not related	Yes
[redacted]	[redacted]	Advagraf+maintained corticosteroid dose	Metabolism and nutrition disorders	Diabetes mellitus	[redacted]	[redacted]	Severe	Recovering	No dose change	Not related	Yes

Coding dictionary: MedDRA 18.1

Source: CSR Table 9.1.2.2-1 Details of Serious Adverse Events

Table 10 Hypertrichosis

Screening No.	Random No.	Group	Visit	Visit Date	Incidence	Severity
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 2	[redacted]	Yes	Minimal
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 6		No	
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 2		Yes	Severe
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 6		Yes	Mild
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 2		Yes	Severe
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 6		No	

Table 11 Gingival hyperplasia

Screening No.	Random No.	Group	Visit	Visit Date	Incidence	Severity
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 2	[redacted]	Yes	Minimal
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 6		No	
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 2		Yes	Moderate
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 6		No	
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 2		Yes	Mild
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 6		No	
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 2		Yes	Mild
[redacted]	[redacted]	Advagraf+50% reduced corticosteroid	Visit 6		No	
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 2		Yes	Severe
[redacted]	[redacted]	Advagraf+maintained corticosteriod dose	Visit 6		No	