Name of Sponsor/Company: Astellas Pharma Europe BV		
Name of Finished Product: Amevive®		
Name of Active Ingredient: Alefacept		

SYNOPSIS

Title of Study: Efficacy and Safety of Alefacept in Combination with Tacrolimus, Mycophenolate Mofetil and Steroids in De-Novo Kidney Transplantation – A Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study

Responsible Medical Officer / Coordinating Investigator: [redacted], MD, PhD / [redacted]

Study Center(s): Thirty in the following countries: Austria = 1; Belgium = 5; Czech Republic = 1; Germany = 1; Spain = 4; France = 7; United Kingdom = 1; Hungary = 1; Italy = 4; The Netherlands = 1; Poland = 3; Sweden = 1

Publication (reference): none to date

Study Period: approximately 2 years

Date of first enrollment (Study initiation date): 20 December 2007

Date of last evaluation (Study completion date): 18 September 2009

Phase of Development: 2

Objectives: The primary objective of this study was to evaluate the efficacy and safety of alefacept in a kidney transplant population. Data obtained from nonhuman primate models suggested that 12 weeks of treatment with alefacept in combination with tacrolimus, MMF and steroids may be more effective than, and as safe as a combination therapy of tacrolimus with MMF and steroids. Efficacy was measured as the occurrence of and time to biopsy proven acute T-cell mediated rejection at 6 months, as assessed locally.

Methodology: This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alefacept as compared to placebo in renal transplant patients 18 to 65 years of age. Patients in both treatment groups received study drug in combination with standard triple immunosuppressive therapy (tacrolimus, MMF and steroids). After screening, eligible patients were randomized (1:1) to receive study drug for 3 months after transplantation, and safety and efficacy parameters were collected during a 6-month study period.

Number of Patients (planned, enrolled and analyzed): The planned sample size was 100 patients per treatment arm (200 patients in total). There were 4 analysis sets defined: the Full Analysis Set (FAS), the Per Protocol Set (PPS), the Safety Analysis Set (SAF) and the Pharmacokinetics Analysis Set (PKAS). There were 110 patients randomized to receive placebo and 108 patients randomized to receive alefacept. The FAS, PPS, SAF and PKAS consisted respectively of 107, 66, 107 and 0 patients in the placebo arm and 105, 58, 105 and 23 patients in the alefacept arm.

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Diagnosis and Main Criteria for Inclusion:

1. Patient with end-stage kidney disease who was a suitable candidate for primary kidney transplantation or re-transplantation.
2. Male or female patient at least 18 years of age and younger than 65 years.
3. Patient receiving a kidney transplant from a non-human leucocyte antigen (HLA) identical living donor or a deceased HLA identical/non-HLA identical donor between 5 and 59 years of age with compatible ABO blood type.

Main exclusion criteria

1. Patient had a panel reactivity antibody grade > 20% in the previous 6 months and/or had had a previous graft survival shorter than 1 year due to immunological reasons.
2. Patient was to receive a kidney transplant from a non-heart beating donor.
3. Patient was to receive a kidney from a 50- to 59-year-old donor with 2 of the following 3 factors: history of hypertension, cerebrovascular accident as cause of death, final pre-procurement serum creatinine > 1.5 mg/dL (United Network for Organ Sharing expanded criteria donor).
4. Cold ischemia time of the donor kidney was ≥ 30 hours.

Test Product, Dose and Mode of Administration, Batch Numbers: Alefacept, from batch number [redacted], in saline for injection administered intravenously (iv) as 7.5 mg (0.25 mL reconstituted solution) on day 0 and day 3 and thereafter subcutaneously (sc) as 15 mg (0.5 mL reconstituted solution) weekly for 12 weeks;

Duration of Treatment: Approximately 12 weeks

Reference Product, Dose and Mode of Administration, Batch Numbers: Placebo (saline solution for injection) administered iv and sc in volumes to match those of alefacept injections

Criteria for Evaluation: The primary efficacy variable was incidence (Kaplan-Meier estimate) of biopsy-confirmed acute T-cell mediated rejection (Banff Grade ≥ 1) as assessed by local reading within the first 6 months following transplantation. Events occurring between completion of transplantation and month 6 (up to study day 182) were used in the analysis.

The secondary efficacy variables were:

1. Incidence of biopsy-confirmed acute T-cell mediated rejection as assessed by central reading
2. Incidence of acute rejections diagnosed by signs and symptoms
3. Incidence of steroid-resistant acute rejections
4. Incidence of biopsy-confirmed acute antibody-mediated rejection

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5. Incidence of biopsy-confirmed acute T-cell mediated OR antibody-mediated rejection
6. Incidence of biopsy-confirmed acute T-cell mediated AND antibody-mediated rejection
7. Patient survival defined as any patient known to be alive at month 6
8. Graft survival defined as any patient who did not experience retransplantation, nephrectomy, death, or dialysis ongoing at end of study or at discontinuation unless superseded by follow-up information
9. Delayed graft function defined as the requirement for dialysis within the first week posttransplant
10. Efficacy failure rate defined as any patient who experienced death, graft loss, biopsy-confirmed acute T-cell mediated rejection as assessed by local reading or loss to follow-up
11. Treatment failure defined as any patient who experienced death, graft loss, biopsy-confirmed acute T-cell mediated as assessed by local reading, loss to follow-up or premature discontinuation of study drug for any reason
12. Serum creatinine concentrations, calculated creatinine clearance (Cockcroft formula) and glomerular filtration rate (GFR) as estimated by Modification of Diet in Renal Disease (MDRD) formula

Safety was primarily assessed based on adverse events (AEs) with emphasis on deaths, infections and malignancies.

Statistical Methods: The Full Analysis Set (FAS) was defined as all randomized and transplanted patients who received at least 1 dose of study drug. The primary analysis was based on the FAS.

The Per Protocol Set (PPS) included all patients of the FAS who had no major protocol violations. Protocol violations occurring after an event of biopsy-confirmed acute T-cell mediated rejection were ignored for purposes of determining PPS eligibility. PPS eligibility was determined before unblinding.

The Safety Analysis Set (SAF) was defined as all randomized patients who received at least 1 dose of study drug. The SAF was used for summaries of all safety and tolerability variables. Adverse events were considered treatment emergent if there was no evidence that the start date was prior to date and time of reperfusion, or the AE worsened after reperfusion. Adverse events with a start date after day 182 were not included in summaries.

For all rejection endpoints, differences between the treatment groups were assessed using the Wilcoxon-Gehan test at a 2-sided 10% significance level. The Kaplan-Meier curves were constructed using the last follow-up visit as censoring time for patients not experiencing a rejection. Patients were analyzed according to the treatment arm to which they were randomized regardless of actual treatment received. In addition, 2-sided 90% CIs for the Kaplan-Meier estimates at month 6 for both treatment arms and for their differences were constructed using the normal approximation with standard error estimated according to Greenwood's formula. This analysis was repeated for the secondary efficacy variables of efficacy failure and treatment failure.

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Graft loss and graft failure was assessed using observed incidence of events with p-value and CI for the difference between arms derived using a Chi-square test and normal approximation, respectively.

Differences between treatment arms in the mean serum creatinine and GFR by MDRD were tested using an analysis of variance model.

Descriptive statistics and frequency counts and percentages were used to summarize patient disposition, demographic and safety variables. Continuous and categorical demographic variables were compared between treatment groups using a t-test and a Chi-square test, respectively.

Summary of Results/Conclusions:

Population: A total of 221 patients were screened, of which 212 were randomized to treatment and received study drug. All 212 patients were included in the FAS; 124 in the PPS, 212 in the SAF, and 23 alefacept-treated patients in the PKAS. No patients were excluded from the FAS; therefore, the FAS and the SAF contain the same patients.

Patient disposition is presented in Table 1.

Table 1: Patient Disposition by Treatment Phase - SAF

Parameter	Patients, n (%)		
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**	**Total (n = 212)**
Month 3 assessment			
Completed treatment	89 (83.2)	83 (79.0)	172 (81.1)
Primary reason for treatment discontinuation			
Adverse Event	6 (5.6)	7 (6.7)	13 (6.1)
Withdrawn consent	0	5 (4.8)	5 (2.4)
Patient lost to follow up	0	0	0
Protocol violation	1 (0.9)	1 (1.0)	2 (0.9)
Graft loss	4 (3.7)	3 (2.9)	7 (3.3)
Discontinued due to rejection	1 (0.9)	2 (1.9)	3 (1.4)
Other	2 (1.9)	2 (1.9)	4 (1.9)
Not fulfilled inclusion or exclusion criteria	4 (3.7)	2 (1.9)	6 (2.8)
Lack of efficacy	0	0	0
Death	0	0	0
Month 6 assessment (end of study)			
Completed study	92 (86.0)	88 (83.8)	180 (84.9)
Reason study discontinuation			
Death	2 (1.9)	1 (1.0)	3 (1.4)
Lost to follow up	1 (0.9)	0	1 (0.5)
Other	8 (7.5)	10 (9.5)	18 (8.5)
Withdrawn consent	4 (3.7)	6 (5.7)	10 (4.7)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set [SAF]).

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Source: Table 12.1.2.1.1and Table 12.1.2.2.2

The 2 treatment arms were comparable in terms of patient demographics, with no statistically significant differences between arms observed for any demographic parameter (Table 2). The mean age for patients in the control group was 47 years and 44 years for the investigational treatment arm. There were more black patients in the control arm (9%) compared to the alefacept arm (4%). The patient demographics were similar in the SAF and PPS populations, with no inherent differences between the 2 treatment arms.

Table 2 Summary of Patient Demographics – SAF

Parameter	Control Arm Placebo (n = 107)	Investigational Arm Alefacept (n = 105)	p-value†
Sex			
Male, n (%)	74 (69.2)	65 (61.9)	0.266
Female, n (%)	33 (30.8)	40 (38.1)	
Race			
White, n (%)	93 (86.9)	97 (92.4)	0.286
Black, n (%)	10 (9.3)	4 (3.8)	
Asian, n (%)	3 (2.8)	4 (3.8)	
Other, n (%)	1 (0.9)	0	
Age (years) n (%)			
18 - 45	44 (41.1)	51 (48.6)	0.275
46 - 65	63 (58.9)	54 (51.4)	
Age Mean (SD)	46.5 (11.3)	44.2 (11.9)	0.159
Weight (kg)			
Mean (SD)	72.50 (15.18)	71.10 (14.62)	0.496
Median (range)	71.70 (39.0-117.0)	72.00 (43.5-115.0)	
Height (cm)			
Mean (SD)	171.4 (9.22)	170.0 (9.47)	0.251
Median (range)	172.0 (148-197)	170.0 (140-196)	

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set [SAF]).

† P-values for continuous variables and categorical variables from a one-way ANOVA and Chi-square test, respectively.

Source: Table 12.1.3.1

Efficacy Results:

The primary endpoint was incidence (Kaplan-Meier estimate) of biopsy-confirmed acute T-cell mediated rejection (Banff Grade ≥ 1) as assessed by local reading within the first 6 months following transplantation; results are displayed in Table 3.

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Table 3: Primary Endpoint Analysis: Comparison of Kaplan-Meier Curves Biopsy Confirmed Acute T-cell Mediated Rejection – FAS

Visit	Control Arm Placebo (n = 107)			Investigational Arm Alefacept (n = 105)		
	Number of Patients with Events	Number of Patients at Risk	Kaplan-Meier Estimate	Number of Patients with Events	Number of Patients at Risk	Kaplan-Meier Estimate
Day 3	0	107	0	0	105	0
Week 1	2	103	0.02	5	100	0.05
Week 2	6	99	0.06	9	95	0.09
Week 3	6	99	0.06	9	94	0.09
Week 4	7	98	0.07	9	93	0.09
Week 5	7	98	0.07	10	92	0.10
Week 6	7	98	0.07	10	91	0.10
Week 7	7	97	0.07	11	90	0.11
Week 8	7	97	0.07	11	90	0.11
Week 9	7	97	0.07	11	90	0.11
Week 10	7	97	0.07	11	90	0.11
Week 11	7	97	0.07	11	90	0.11
Week 12	7	97	0.07	11	90	0.11
Month 4	7	97	0.07	11	89	0.11
Month 5	7	96	0.07	11	88	0.11
Month 6	7	95	0.07	11	85	0.11

All randomized and transplanted patients who received at least 1dose of study drug (Full Analysis Set [FAS]).
Source: Table 12.3.1.1.1

The primary endpoint resulted in an incidence of acute rejections of 11 % in the investigational group vs. 7 % in the control group (p = 0.309). All of the biopsy-confirmed acute T-cell mediated rejections occurred in the first 7 weeks after reperfusion (none observed after Day 49), most occurred in the first 2 weeks. For placebo and alefacept, respectively, there were 2 and 5 events in week 1, and 4 events each in week 2. Eight of the 11 rejections in the investigational arm and 4 of the 7 rejections in the control arm were of Grade IIA or IIB.

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Table 4: Overview of Select Rejection Endpoint Results

Type of Rejection – Analysis Set, Location of Biopsy Reading	Kaplan-Meier Estimates Events, 6-Month Failure Rate (90% CI)†		Wilcoxon-Gehan test p-value‡
	Control Arm Placebo (n = 107, FAS) (n = 66, PPS)	Investigational Arm Alefacept (n = 105, FAS) (n = 58, PPS)	
Biopsy-confirmed acute T-cell mediated rejections – FAS, local review (primary)	7, 0.07 (0.03, 0.11)	11, 0.11 (0.06, 0.16)	0.309
Biopsy-confirmed acute T-cell mediated rejections – PPS, local review	6, 0.09 (0.03, 0.15)	6, 0.10 (0.04, 0.17)	0.806
Biopsy-confirmed acute T-cell mediated rejections – FAS, central review	10, 0.10 (0.05, 0.14)	8, .08 (0.03, 0.12)	0.671
Biopsy-confirmed acute T-cell mediated rejections – PPS, central review	6, 0.09 (0.03, 0.15)	3, 0.05 (0.004, 0.10)	0.388
Acute rejections, diagnosed by signs and symptoms – FAS, local review	29, 0.27 (0.20, 0.35)	23, 0.22 (0.16, 0.29)	0.323
Acute rejections, diagnosed by signs and symptoms – PPS, local review	20, 0.31 (0.21, 0.40)	11, 0.19 (0.11, 0.27)	0.121
Clinically treated acute rejections – FAS, local review	26, 0.25 (0.18, 0.32)	16, 0.15 (0.10, 0.21)	0.104
Clinically treated acute rejections – PPS, local review	18, 0.28 (0.19, 0.37)	8, 0.14 (0.06, 0.21)	0.077
Steroid-resistant acute rejections – FAS, local review	8, 0.08 (0.03, 0.12)	6, 0.06 (0.02, 0.10)	0.620
Steroid-resistant acute rejections – PPS, local review	4, 0.06 (0.01, 0.11)	3, 0.05 (0.004, 0.10)	0.830
Biopsy confirmed acute antibody-mediated rejections – FAS, local review	3, 0.03 (0.002, 0.055)	4, 0.04 (0.007, 0.069)	0.696
Biopsy confirmed acute antibody-mediated rejections – PPS, local review	1, 0.02 (0, 0.040)	1, 0.02 (0, 0.045)	0.945
Biopsy confirmed acute T-cell mediated or antibody-mediated rejections – FAS, local review	10, 0.10 (0.05, 0.14)	13, 0.13 (0.07, 0.18)	0.485

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Type of Rejection – Analysis Set, Location of Biopsy Reading	Kaplan-Meier Estimates Events, 6-Month Failure Rate (90% CI)†		Wilcoxon-Gehan test p-value‡
	Control Arm Placebo (n = 107, FAS) (n = 66, PPS)	Investigational Arm Alefacept (n = 105, FAS) (n = 58, PPS)	
Biopsy confirmed acute T-cell mediated or antibody-mediated rejections – PPS, local review	7, 0.11 (0.04, 0.17)	7, 0.12 (0.05, 0.19)	0.811
Borderline T-cell mediated or biopsy confirmed acute T-cell mediated or antibody-mediated rejections – FAS, local review	21, 0.20 (0.14, 0.27)	17, 0.16 (0.10, 0.22)	0.487
Borderline T-cell mediated or biopsy confirmed acute T-cell mediated or antibody-mediated rejections – PPS, local review	12, 0.19 (0.11, 0.26)	8, 0.14 (0.06, 0.21	0.503
Biopsy confirmed acute mixed T-cell mediated and antibody-mediated rejections – FAS, local review	0, 0 (0, 0)	1, 0.010 (0, 0.025)	0.317
Biopsy confirmed acute mixed T-cell mediated and antibody-mediated rejections – PPS, local review	0, 0 (0, 0)	0, 0 (0, 0)	-

All randomized and transplanted patients who received at least 1dose of study drug (Full Analysis Set [FAS]).
All patients of the FAS who had no major protocol violations (Per Protocol Set [PPS]).

† Obtained from normal approximation using Greenwood's formula
‡ Primary p-value

Source: Tables 12.3.1.1.1, 12.3.1.2.1, 12.3.2.1.1, 12.3.2.1.2, 12.3.2.2.1, 12.3.2.2.2, 12.3.2.3.1, 12.3.2.3.2, 12.3.2.4.1, 12.3.2.4.2, 12.3.1.1.2, 12.3.1.2.2, 12.3.1.1.4, 12.3.1.2.4, 12.3.1.5.1, 12.3.1.5.2, 12.3.1.1.3 and 12.3.1.2..3

Patient Survival and Graft Function

Alefacept was not statistically superior to placebo in the rate of patient survival. In the FAS, the Kaplan-Meier estimated rates of patient survival at month 6 post-transplantation were 97% and 99% for the control arm and investigational arm, respectively, with the difference between treatment associated with a p-value of 0.350.

The incidence of delayed graft function (defined as the requirement for dialysis within the first week post-transplant) was higher in the control arm than in the investigational arm (12.1% versus 7.6%), this difference was not statistically significant (p = 0.270).

The incidence of graft loss (defined as retransplantation, nephrectomy and death or as dialysis ongoing at end of study or at discontinuation unless superceded by follow-up information) was 4.8% in the investigational arm and 9.3% in the control arm (p = 0.193). Most of the graft losses for both treatment arms occurred within the first week of treatment.

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Efficacy and Treatment Failures

There were numerically more efficacy failures (defined as death, graft loss, biopsy-confirmed acute T-cell mediated rejection assessed by local reading or lost to follow-up) in the investigational arm (21%; 90% CI: 0.09, 0.21) than in the control arm (15%; 90% CI: 0.14, 0.27). The difference in treatment arms over 6 months was associated with a p-value of 0.279.

The 6-month treatment failure event rate (defined as death, graft loss or biopsy-confirmed acute T-cell mediated rejection assessed by local reading, lost to follow-up) or discontinuation of alefacept/placebo at any time for any reason was 21% (90% CI: 0.14, 0.27) in the control arm and 26% (90% CI: 0.19, 0.33) in the investigational arm, with the difference in treatment arms over 6 months associated with a p-value of 0.389.

The higher rate of efficacy failures and treatment failures in the investigational arm can be explained by a higher rate of patients in the investigational arm who were lost to follow-up, i.e. who dropped out of the study prematurely and did not attend the follow-up visit which was planned to take place 6 months after the start of treatment.

Renal Function:

A summary of the serum creatinine and GFR as estimated by MDRD is provided in Table 5 for selected visits.

Table 5: Mean Serum Creatinine and GFR by MDRD - FAS

Variable / Time Point	Control Arm Placebo (n = 107)	Investigational Arm Alefacept (n = 105)	p-value†
Serum Creatinine (mcmol/L)			
Month 1	153.5	140.6	0.380
Month 3	133.5	130.0	0.691
Month 6	126.1	123.5	0.662
GFR by MDRD (mL/min/1.73m^2)			
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**	**p-value†**
Month 1	53.6	56.4	0.405
Month 3	58.2	57.5	0.826
Month 6	58.4	59.4	0.744

All randomized and transplanted patients who received at least 1dose of study drug (Full Analysis Set [FAS]).
GFR: glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.
† Analysis of variance model
Source: Table s 12.3.2.12.1.1 and 12.3.2.13.1.1

For serum creatinine, no statistically significant differences were observed at month 1, 3 or 6 as evidenced by no p-value being less than 0.10. GFR by MDRD showed no statistically significant differences at any visit as evidenced by no p-value being less than 0.10.

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Safety Results:

In accordance with the protocol, all rejections, as well as all BK, EBV and CMV infections, were reported as an SAE. In this report, the preferred term Kidney Transplant Rejection was not included in tables of adverse events as these were considered efficacy endpoints and are summarized in the Efficacy section.

The overall incidence of AEs (reported in at least 5% of patients), regardless of relationship to treatment drug, is shown in Table 6. Most AEs occurred with a similar rate between the 2 treatment arms, with the following exceptions: cytomegalovirus viremia, cytomegalovirus infections, hypertension, tremor and tachycardia were more frequent in the investigational arm, while BK virus infection, hypophosphatemia, anemia and histology abnormal were more common in the control arm.

There were some imbalances between treatment arms in AEs considered to be related to study drug; slightly more infection and infestation AEs were considered drug-related in the control arm than in the investigational arm; blood and lymphatic system disorders were more frequently considered drug-related in the investigational arm.

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Table 6: Overall Incidence of Treatment-emergent Adverse Events Regardless of Relationship to Study Medication Occurring in ≥ 5% of Patients in Either Arm - SAF

MedDRA (v11.0) System Organ Class Preferred Term	**Patients, n (%)**	
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**
Overall (Any Adverse Event)	**102 (95.3)**	**101 (96.2)**
Infections and infestations	**62 (57.9)**	**64 (61.0)**
Urinary tract infection	27 (25.2)	28 (26.7)
Cytomegalovirus infection	6 (5.6)	9 (8.6)
Cytomegalovirus viraemia	2 (1.9)	6 (5.7)
BK virus infection	8 (7.5)	3 (2.9)
Metabolism and nutrition disorders	**63 (58.9)**	**62 (59.0)**
Hyperglycaemia	14 (13.1)	17 (16.2)
Hypokalaemia	17 (15.9)	15 (14.3)
Diabetes mellitus	14 (13.1)	14 (13.3)
Hyperkalaemia	10 (9.3)	10 (9.5)
Hypomagnesaemia	6 (5.6)	7 (6.7)
Hyperlipidaemia	7 (6.5)	6 (5.7)
Hypocalcaemia	7 (6.5)	6 (5.7)
Hyperuricaemia	7 (6.5)	5 (4.8)
Hypercholesterolaemia	7 (6.5)	4 (3.8)
Hypophosphataemia	8 (7.5)	2 (1.9)
Gastrointestinal disorders	**63 (58.9)**	**61 (58.1)**
Diarrhoea	30 (28.0)	28 (26.7)
Constipation	20 (18.7)	19 (18.1)
Nausea	7 (6.5)	10 (9.5)
Vomiting	7 (6.5)	8 (7.6)
Abdominal pain upper	5 (4.7)	8 (7.6)
Abdominal pain	4 (3.7)	7 (6.7)
Blood and lymphatic system disorders	**67 (62.6)**	**60 (57.1)**
Anaemia	54 (50.5)	43 (41.0)
Leukopenia	15 (14.0)	14 (13.3)
Thrombocytopenia	7 (6.5)	6 (5.7)
Renal and urinary disorders	**46 (43.0)**	**38 (36.2)**
Renal impairment	13 (12.1)	12 (11.4)
Renal tubular necrosis	6 (5.6)	5 (4.8)
Dysuria	7 (6.5)	4 (3.8)
Investigations	**37 (34.6)**	**37 (35.2)**
Blood creatinine increased	10 (9.3)	11 (10.5)
Histology abnormal	11 (10.3)	6 (5.7)

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MedDRA (v11.0) System Organ Class Preferred Term	**Patients, n (%)**	
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**
Injury, poisoning and procedural complications	**47 (43.9)**	**36 (34.3)**
Complications of transplanted kidney	20 (18.7)	18 (17.1)
Graft dysfunction	7 (6.5)	4 (3.8)
Procedural pain	6 (5.6)	3 (2.9)
Vascular disorders	**29 (27.1)**	**34 (32.4)**
Hypertension	19 (17.8)	25 (23.8)
Lymphocele	9 (8.4)	3 (2.9)
General disorders and administration site conditions	**37 (34.6)**	**27 (25.7)**
Oedema peripheral	14 (13.1)	10 (9.5)
Pyrexia	11 (10.3)	10 (9.5)
Nervous system disorders	**17 (15.9)**	**24 (22.9)**
Tremor	8 (7.5)	16 (15.2)
Headache	4 (3.7)	7 (6.7)
Psychiatric disorders	**25 (23.4)**	**19 (18.1)**
Insomnia	12 (11.2)	11 (10.5)
Anxiety	7 (6.5)	4 (3.8)
Skin and subcutaneous tissue disorders	**13 (12.1)**	**14 (13.3)**
Pruritus	6 (5.6)	4 (3.8)
Cardiac disorders	**11 (10.3)**	**11 (10.5)**
Tachycardia	1 (0.9)	6 (5.7)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set [SAF]).
Source: Table 12.6.1.2.1

As anticipated, commensurate with the study population, infections and infestations were the most commonly reported serious adverse events (SAEs) in both treatment groups (reported in 26.2% and 23.8% of patients in the control and investigational arms, respectively) (Table 7) and were the most commonly reported serious adverse events considered as related to study drug (Table 8).

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Table 7: Overall Incidence of Serious Adverse Events Regardless of Relationship to Study Medication Occurring in ≥ 5% of Patients in Either Arm - SAF

MedDRA (v11.0) System Organ Class Preferred Term	**Patients, n (%)**	
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**
Overall (Any Adverse Event)	**62 (57.9)**	**57 (54.3)**
Infections and infestations	**28 (26.2)**	**25 (23.8)**
Urinary tract infection	6 (5.6)	2 (1.9)
Cytomegalovirus infection	6 (5.6)	9 (8.6)
BK virus infection	8 (7.5)	3 (2.9)
Renal and urinary disorders	**14 (13.1)**	**17 (16.2)**
Renal impairment	8 (7.5)	4 (3.8)
Investigations	**17 (15.9)**	**8 (7.6)**
Histology abnormal	11 (10.3)	6 (5.7)
Injury, poisoning and procedural complications	**17 (15.9)**	**14 (13.3)**
Complications of transplanted kidney	8 (7.5)	8 (7.6)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set [SAF]).

Source: Table 12.6.1.7

Table 8: Overall Incidence of Serious Adverse Events Assessed as Being Related to Study Drug Occurring in ≥ 2% Patients - SAF

MedDRA (v11.0) System Organ Class Preferred Term	**Patients, n (%)**	
	Control Arm Placebo (n = 107)	**Investigational Arm Alefacept (n = 105)**
Overall (Any Adverse Event)	**19 (17.7)**	**16 (15.2)**
Infections and infestations	**13 (12.1)**	**12 (11.4)**
Cytomegalovirus infection	4 (3.7)	5 (4.7)
BK virus infection	2 (1.8)	3 (2.8)
Investigations	**4 (3.7)**	**3 (2.8)**
Histology abnormal	3 (2.8)	2 (1.9)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set [SAF]).

Causally related was defined possible or probable, as assessed by the Investigator, or records where relationship is missing.

Source: Table 12.6.1.8.1

The overall incidence of SAEs was comparable between the treatment arms, and the types of SAEs reported were generally similar with the exception of investigations (15.9% for the control arm versus 7.6% for the investigational arm).

Name of Sponsor/Company: Astellas Pharma Europe BV		
Name of Finished Product: Amevive®		
Name of Active Ingredient: Alefacept		

Malignancies

There were 7 neoplasms in the alefacept arm and 1 in the placebo arm. One of the 7 neoplasms in the alefacept arm, seborrhoeic keratosis, was not a malignancy.

Deaths

A total of 4 patients died during the study period, 3 in the placebo arm and 1 in the alefacept arm. All of the deaths were considered by the investigator to be not related to alefacept/placebo. In the placebo arm, the primary cause of death was reported as "septic shock" in 2 patients and "acute pulmonary edema" in 1 patient. The primary cause of the death case for the patient in the alefacept arm was "lung neoplasm malignant".

CONCLUSIONS:

Although the basic mode of action of alefacept was observed as shown by significant reductions in memory T-cells, a beneficial effect of alefacept administered in addition to the standard triple immunosuppressive therapy consisting of tacrolimus, MMF and steroids could not be proven in this study. However, borderline acute T-cell mediated rejections showed a favorable numerical result for the investigational (i.e., alefacept) arm as compared to the control arm. Although no clear benefit in terms of efficacy could be proven for the addition of alefacept to the standard triple immunosuppressive regimen, the results at least showed that the mode of action of alefacept does not interfere with standard immunosuppressive treatment.

More cytomegalovirus infections occurred in the alefacept arm as compared to the placebo arm, however for BK infections the reverse trend was observed. Therefore, these results can be considered inconclusive and interpretation might be difficult. For malignancies, a higher incidence was reported in the treatment arm, but most tumors were most likely pre-existing to the study. Additional long-term studies would be needed to fully characterize the occurrence of malignancies in patients treated with alefacept added to standard triple immunosuppressive therapy.

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