Sponsor

Novartis

Generic Drug Name

Sotrastaurin (AEB071)

Therapeutic Area of Trial

Kidney transplantation

Approved Indication

None

Protocol Number

CAEB071A2214

Title

A partially blinded, prospective, randomized multicenter study evaluating efficacy, safety and tolerability of oral sotrastaurin plus standard or reduced exposure tacrolimus vs. Mycophenolic acid plus tacrolimus in de novo renal transplant recipients.

Study phase

Phase II

Study Start/End Dates

15-Dec-2009 (first patient first visit) to 02-Aug-2012 (last patient last visit)

Early termination date: 27-Mar-2012 (as AEB071 did not show sufficient therapeutic benefit)

Study Design/Methodology

This study was a 3-year, randomized, multicenter, partially blinded, 4-arm study comparing the efficacy and evaluating the safety of oral sotrastaurin + standard or reduced exposure tacrolimus (Prograf®) versus the active control Myfortic (MPA) + standard exposure tacrolimus for initial and maintenance prophylaxis of organ rejection in adult *de novo* renal transplant patients. The study population consisted of male and female *de novo* adult renal transplant patients (approximately75 per treatment arm) who were randomized (1:1:1:1) to one of the 4 treatment arms within 24 hours following transplantation.

Centers

A total of 44 centers in 15 countries

Publication

None

Test Product (s), Dose(s), and Mode(s) of Administration

AEB071 25 mg and AEB071 100 mg or matching placebo hard gelatin capsules for oral administration.

The dose of sotrastaurin for treatment arms 1, 2 and 3 is given below:

Arm 1: AEB071 100 mg b.i.d. + standard exposure tacrolimus

Arm 2: AEB071 200 mg b.i.d. + standard exposure tacrolimus

Arm 3: AEB071 300 mg b.i.d. + reduced exposure tacrolimus

Arm 4 (control arm): Myfortic 720 mg b.i.d. + standard exposure tacrolimus

Statistical Methods

The full analysis set (FAS) consisted of all randomized patients. Following the intent-to-treat (ITT) principle, patients were analyzed according to the treatment they were assigned to at randomization. All analyses based on the FAS used all available data – 'all event analysis'. For selected sensitivity analyses of efficacy endpoints, 'on-treatment' analysis (including all assessments up to 7 days after study drug discontinuation) based on the full analysis set was performed. The per protocol (PP) analysis set consisted of all patients in the FAS who complete the study without any major deviations from protocol procedures. The safety analysis set consisted of all patients who received at least one dose of study drug. Patients were analyzed according to the treatment they received. For selected variables, 'on-treatment analysis' was applied: e.g. for AEs/infections assessments within 7 days, for SAEs assessments within 30 days and for laboratory/ECG/vital signs data assessments within 2 days after study drug discontinuation are analyzed only.

Baseline patient information was summarized by treatment group for the FAS, using frequency distributions for categorical variables and descriptive statistics (mean, standard deviation, median, minimum and maximum) for continuous variables.

The primary objective was to demonstrate non-inferiority of at least one of the AEB071 arms compared to the control arm (MPA & tacrolimus) with respect to composite efficacy failure (treated BPAR, graft loss, death or loss to follow-up) at Month 6. The primary efficacy analysis used Kaplan-Meier methodology (Kaplan and Meier 1958) to estimate event rates using the FAS. Greenwood's formula was used to estimate standard errors and to derive the two-sided 95% confidence interval (CI) from the Z-test statistic distribution for the difference in event rates between the AEB071 and control arms. The upper bound of the confidence interval was evaluated against a non-inferiority (NI) margin of 15%. A NI margin of 15% was higher than typically justified in phase III sized trials, but was operationally feasible for a phase II trial in transplantation. As this was a phase II study, no multiplicity adjustments was made. A sample size of n=75 per group was chosen to ensure sufficient evidence of noninferiority between STN and control group over the range of expected event rates (6 to 10% in the control group at Month 6).

The secondary efficacy variables were analyzed at Months 3, 6 and 12 using Kaplan-Meier methodology to estimate event rates, difference in event rates and associated 95% CI between the AEB071 and control arms as described for the primary efficacy endpoint.

Safety and tolerability was assessed by statistical and/or clinical review of all safety parameters, including SAEs, renal function parameters, discontinuations due to adverse events, laboratory values, vital signs, CNI-specific signs and symptoms, and ECG abnormalities. All analyses were based on the safety analysis set.

Descriptive statistics were presented for calculated eGFR (MDRD), creatinine and estimated creatinine clearance. Values were compared between treatment groups using the Wilcoxon Rank Sum test supported by the estimate and 95% CI for the location shift between AEB071 groups and the control group (Hodges-Lehman estimator) for on-treatment assessments.

Interim analysis

This study planned for one primary analysis and three follow-up analyses in addition to quarterly interim reviews of safety and efficacy by the DMC (further details of the operation and scope of the DMC are provided separately in the DMC Charter). The primary analysis included all patients up to visit Month 6. The first follow-up analysis was performed on all patients and up to visit Month 12. Due to the premature termination of the AEB071 program and of this study, the second Month 24 follow-up analysis was not performed but instead one final analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients eligible for inclusion in this study had to fulfill all of the following criteria:

- Provide written informed consent before any assessment is performed.
- Male or female ≥ 18 years old.
- Recipient of a first or second kidney transplant from a deceased, living unrelated or nonhuman leukocyte antigen (HLA) identical living related donor.
- Recipient of a kidney with a cold ischemia time (CIT) < 30 hours.
- Recipient of a kidney from a donor 10 - 65 years old.

Exclusion criteria:

Patients fulfilling any of the following criteria were not eligible for inclusion in this study:

- recipients who were unable to receive the first dose of oral study medication within 24 hours after allograft reperfusion
- multi-organ transplant recipients
- recipients of an organ from a non-heart beating donor
- patients receiving a second kidney allograft if the first allograft was functional for less than three years
- patients who were treated with drugs that are strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) at screening
- patients with increased cardiac risk
- Patients at high immunological risk.
- Other protocol defined exclusion criteria was applied.

Participant Flow

Patient disposition - n (%) of patients (Full analysis set)

Disposition Reason	AEB 100 mg + TAC SE N=77 n (%)	AEB 200 mg + TAC SE N=73 n (%)	AEB 300 mg + TAC RE N=75 n (%)	MPA 720 mg + TAC SE N=73 n (%)

Completed study*	7 (9.1)	7 (9.6)	6 (8.0)	7 (9.6)
Discontinued study medication				
Total	77 (100.0)	72 (98.6)	70 (93.3)	70 (95.9)
Adverse Event(s)	8 (10.4)	15 (20.5)	26 (34.7)	22 (30.1)
Abnormal laboratory value(s)	1 (1.3)	2 (2.7)	0	0
Abnormal test procedure result(s)	4 (5.2)	1 (1.4)	0	0
Unsatisfactory therapeutic effect	6 (7.8)	0	1 (1.3)	2 (2.7)
Subject withdrew consent	2 (2.6)	1 (1.4)	1 (1.3)	1 (1.4)
Lost to follow-up	0	0	1 (1.3)	1 (1.4)
Administrative problems	54 (70.1)	49 (67.1)	41 (54.7)	43 (58.9)
Death	0	3 (4.1)	0	0
Graft loss	0	1 (1.4)	0	1 (1.4)
Retransplantation	0	0	0	0
Protocol deviation	2 (2.6)	0	0	0
Discontinued study				
Total	70 (90.9)	66 (90.4)	69 (92.0)	66 (90.4)
Subject withdrew consent	7 (9.1)	1 (1.4)	6 (8.0)	2 (2.7)
Lost to follow-up	2 (2.6)	0	2 (2.7)	1 (1.4)
Administrative problems	59 (76.6)	59 (80.8)	60 (80.0)	63 (86.3)
Death	1 (1.3)	6 (8.2)	1 (1.3)	0
Missing	1 (1.3)	0	0	0

The percentages are based on the number of patients in Full Analysis set.

*Data entry issue, no patients completed the full 36 month duration of the study due to the DMC's recommendation for discontinuing AEB071 100 mg arm early and later the sponsor's decision to prematurely terminate the study – both recorded as 'Administrative problems'.

Baseline Characteristics

Recipient demographic and disease characteristics summary (Full analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Age (years)				
n	77	73	75	73
Mean	46.4	48.6	46.2	47.0
SD	12.93	13.06	13.57	12.33
Median	46.0	50.0	48.0	48.0
Range	19, 71	24, 77	20, 73	21, 75
Age group - n (%)				
<65	71 (92.2)	64 (87.7)	70 (93.3)	69 (94.5)
≥65	6 (7.8)	9 (12.3)	5 (6.7)	4 (5.5)
Gender - n (%)				
Male	51 (66.2)	50 (68.5)	42 (56.0)	52 (71.2)
Female	26 (33.8)	23 (31.5)	33 (44.0)	21 (28.8)

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Race - n (%)				
Caucasian	59 (76.6)	61 (83.6)	59 (78.7)	59 (80.8)
Black	3 (3.9)	2 (2.7)	4 (5.3)	2 (2.7)
Asian	12 (15.6)	3 (4.1)	9 (12.0)	7 (9.6)
Native American	0	0	0	0
Pacific islander	0	0	0	0
Other	3 (3.9)	7 (9.6)	3 (4.0)	5 (6.8)
End stage disease leading to transplantation - n (%)				
Glomerulonephritis / glomerular disease	11 (14.3)	16 (21.9)	14 (18.7)	12 (16.4)
Pyelonephritis	2 (2.6)	0	0	1 (1.4)
Polycystic disease	14 (18.2)	10 (13.7)	17 (22.7)	14 (19.2)
Hypertension / nephrosclerosis	9 (11.7)	5 (6.8)	7 (9.3)	14 (19.2)
Drug induced toxicity	0	0	0	1 (1.4)
Diabetes mellitus	7 (9.1)	3 (4.1)	2 (2.7)	5 (6.8)
Interstitial nephritis	1 (1.3)	3 (4.1)	3 (4.0)	1 (1.4)
Vasculitis	0	1 (1.4)	0	0
Obstructive disorder / reflux	1 (1.3)	2 (2.7)	2 (2.7)	2 (2.7)
Renal hyperplasia / dysplasia	1 (1.3)	0	1 (1.3)	0
IgA nephropathy	5 (6.5)	6 (8.2)	5 (6.7)	7 (9.6)
Unknown	11 (14.3)	13 (17.8)	10 (13.3)	8 (11.0)
Other	15 (19.5)	14 (19.2)	14 (18.7)	8 (11.0)
Current Dialysis - n (%)				
Hemodialysis	48 (62.3)	51 (69.9)	46 (61.3)	54 (74.0)
Peritoneal dialysis	18 (23.4)	13 (17.8)	13 (17.3)	11 (15.1)
None	11 (14.3)	9 (12.3)	16 (21.3)	8 (11.0)
Panel reactive antibodies - most recent evaluation (%)				
≤ 5%	70 (90.9)	64 (87.7)	69 (92.0)	71 (97.3)
> 5%	6 (7.8)	8 (11.0)	6 (8.0)	2 (2.7)
n	76	72	75	73
Mean	1.6	1.5	1.0	0.6
SD	5.16	4.09	3.01	2.76
Median	0.0	0.0	0.0	0.0
Range	0, 29	0, 21	0, 20	0, 20
Panel reactive antibodies - peak evaluation (%)				
n	76	72	75	73
Mean	2.8	1.7	2.9	1.2
SD	6.94	4.12	11.99	3.90
Median	0.0	0.0	0.0	0.0
Range	0, 29	0, 21	0, 99	0, 23
Total Number of HLA Mismatches (Locus A, B, or DR)				
n	76	73	75	73
Mean	3.0	2.9	3.2	3.1
SD	1.51	1.55	1.42	1.53
Median	3.0	3.0	3.0	3.0
Range	0, 6	0, 6	0, 6	0, 6

Number of previous renal transplantations				
0	71 (92.2)	66 (90.4)	67 (89.3)	66 (90.4)
1	6 (7.8)	7 (9.6)	8 (10.7)	7 (9.6)
2	0	0	0	0
>2	0	0	0	0
Cold ischemia time (h)				
n	44	43	44	42
Mean	13.2	16.0	14.2	14.2
SD	5.71	6.03	4.53	6.23
Median	13.2	16.4	13.5	14.9
Range	3, 27	5, 27	5, 25	1, 29

Donor characteristics (Full analysis set)

		AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Donor Age (years)	n	77	73	75	73
	Mean	46.5	45.6	46.2	45.5
	SD	10.72	12.39	12.21	12.09
	Median	48.0	48.0	49.0	47.0
	Range	20, 64	9, 64	16, 63	22, 65
Donor characteristic - n (%)	Living related	17 (22.1)	20 (27.4)	20 (26.7)	23 (31.5)
	Living unrelated	15 (19.5)	9 (12.3)	10 (13.3)	8 (11.0)
	Deceased heart beating	45 (58.4)	44 (60.3)	45 (60.0)	42 (57.5)
	Deceased non-heart beating	0	0	0	0

Outcome measures

Primary outcome measures: Occurrence of (composite) efficacy failure defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss, death, or loss to follow-up (LTFU) at Month 6 post-transplantation.

Secondary outcome measures: Occurrence of (composite) efficacy failure and occurrence of individual components (and combinations of the individual components) of the (composite) efficacy failure at various time points (Months 6, 12, 24 and 36 post-transplantation).
- renal allograft function post-transplantation (estimated GFR by MDRD equation; estimated creatinine clearance by Cockroft-Gault formula; serum creatinine).
- safety and tolerability (adverse events, serious adverse events, laboratory abnormalities, vital signs, electrocardiograms, physical examination).

Primary Outcome Result(s)

Analysis of the primary efficacy failure event at Month 6 (Full analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Composite efficacy failure				
Number of events	12	8	9	8
K-M failure rate (%)	16.2	11.0	12.1	11.1
95% CI (%) for K-M estimate	(7.8, 24.6)	(3.8, 18.1)	(4.7, 19.5)	(3.9, 18.4)
Diff (AEB-MPA) Rate (95%CI)	5.1 (-6.0, 16.2)	-0.2 (-10.4, 10.0)	1.0 (-9.4, 11.4)	
Treated BPAR				
Number of events	12	3	7	8
K-M failure rate (%)	16.2	4.2	9.6	11.1
95% CI (%)for K-M estimate	(7.8, 24.6)	(0.0, 8.8)	(2.8, 16.4)	(3.9, 18.4)
Diff (AEB-MPA) Rate (95%CI)	5.1 (-6.0, 16.2)	-7.0 (-15.6, 1.6)	-1.5 (-11.5, 8.4)	
Graft loss				
Number of events	2	2	1	0
K-M failure rate (%)	2.7	2.8	1.4	0.0
95% CI (%) for K-M estimate	(0.0, 6.5)	(0.0, 6.5)	(0.0, 4.0)	(0.0, 0.0)
Diff (AEB-MPA) Rate (95%CI)	2.7 (-1.0, 6.5)	2.8 (-1.0, 6.5)	1.4 (-1.3, 4.0)	
Death				
Number of events	0	4	1	0
K-M failure rate (%)	0.0	5.5	1.3	0.0
95% CI (%) for K-M estimate	(0.0, 0.0)	(0.3, 10.7)	(0.0, 3.9)	(0.0, 0.0)
Diff (AEB-MPA) Rate (95%CI)	0.0 (0.0, 0.0)	5.5 (0.3, 10.7)	1.3 (-1.3, 3.9)	
Loss to follow-up				
Number of events	0	0	0	0
K-M failure rate (%)	0.0	0.0	0.0	0.0
95% CI (%) for K-M estimate	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Diff (AEB-MPA) Rate (95%CI)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	

1. BPAR: biopsy-proven acute rejection
2. Composite efficacy failure: Treated BPAR, graft loss, death, or lost to follow-up
3. K-M = Kaplan-Meier, negative differences favor AEB. CI=Confidence interval

The majority of the composite efficacy failure events occurred within the first 2 months of randomized study medication across all treatment arms. The event rates for AEB071 200 and 300 mg arms appeared to be comparable with the control arm at Month 6, but the event rate for the AEB071 100 mg group appeared to be higher than the control arm at Month 6.

Also, the composite efficacy event rates for AEB071 200 and 300 mg arms appeared to be comparable to control across all time points, while AEB071 100 mg appeared to be worse than the control arm throughout the study.

Secondary Outcome Result(s)

Analysis of the primary composite efficacy failure and tBPAR events at Month 12 (Full analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Composite efficacy failure				
Number of events	14	9	11	10
K-M failure rate (%)	18.9	12.4	14.9	14.0
95% CI (%) for K-M estimate	(10.0, 27.8)	(4.8, 19.9)	(6.8, 23.0)	(5.9, 22.0)
Diff (AEB-MPA) Rate (95%CI)	5.0 (-7.0, 17.0)	-1.6 (-12.6, 9.4)	1.0 (-10.5, 12.4)	
Treated BPAR				
Number of events	14	3	8	9
K-M failure rate (%)	18.9	4.2	11.1	12.5
95% CI (%) for K-M estimate	(10.0, 27.8)	(0.0, 8.8)	(3.8, 18.3)	(4.9, 20.2)
Diff (AEB-MPA) Rate (95%CI)	6.4 (-5.4, 18.1)	-8.4 (-17.3, 0.6)	-1.5 (-12.0, 9.1)	

Safety Results

Adverse Events by System Organ Class

Number (%) of patients reporting AEs by system organ class (Safety analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Total number of patients with AEs	76 (98.7)	73 (100.0)	75 (100.0)	72 (98.6)
Gastrointestinal disorders	63 (81.8)	57 (78.1)	62 (82.7)	56 (76.7)
Infections and infestations	48 (62.3)	55 (75.3)	59 (78.7)	50 (68.5)
Metabolism and nutrition disorders	54 (70.1)	55 (75.3)	44 (58.7)	49 (67.1)
Injury, poisoning and procedural complications	39 (50.6)	35 (47.9)	52 (69.3)	40 (54.8)
Investigations	35 (45.5)	35 (47.9)	33 (44.0)	34 (46.6)

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General disorders and administration site conditions	36 (46.8)	36 (49.3)	31 (41.3)	31 (42.5)
Renal and urinary disorders	31 (40.3)	37 (50.7)	29 (38.7)	32 (43.8)
Vascular disorders	31 (40.3)	38 (52.1)	28 (37.3)	29 (39.7)
Nervous system disorders	35 (45.5)	34 (46.6)	27 (36.0)	29 (39.7)
Blood and lymphatic system disorders	17 (22.1)	28 (38.4)	38 (50.7)	31 (42.5)
Skin and subcutaneous tissue disorders	31 (40.3)	23 (31.5)	29 (38.7)	27 (37.0)
Musculoskeletal and connective tissue disorders	25 (32.5)	26 (35.6)	24 (32.0)	25 (34.2)
Respiratory, thoracic and mediastinal disorders	16 (20.8)	24 (32.9)	25 (33.3)	26 (35.6)
Psychiatric disorders	20 (26.0)	18 (24.7)	24 (32.0)	23 (31.5)
Cardiac disorders	11 (14.3)	24 (32.9)	22 (29.3)	15 (20.5)
Reproductive system and breast disorders	12 (15.6)	7 (9.6)	14 (18.7)	5 (6.8)
Immune system disorders	7 (9.1)	7 (9.6)	6 (8.0)	8 (11.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.6)	8 (11.0)	11 (14.7)	7 (9.6)
Ear and labyrinth disorders	5 (6.5)	4 (5.5)	8 (10.7)	4 (5.5)
Eye disorders	11 (14.3)	4 (5.5)	3 (4.0)	2 (2.7)
Endocrine disorders	2 (2.6)	3 (4.1)	3 (4.0)	3 (4.1)
Congenital, familial and genetic disorders	2 (2.6)	3 (4.1)	2 (2.7)	3 (4.1)
Hepatobiliary disorders	1 (1.3)	4 (5.5)	1 (1.3)	1 (1.4)
Surgical and medical procedures	2 (2.6)	1 (1.4)	1 (1.3)	0
Pregnancy, puerperium and perinatal conditions	2 (2.6)	0	0	0
Social circumstances	0	1 (1.4)	0	0

AEs suspected to be related to the study drug were reported by 51.9%, 65.8% and 70.7% of the patients in the AEB071 100 mg, 200 mg and 300 mg arms respectively. In the control arm, suspected drug-related AEs were reported in 71.2% of the patients.

A patient with multiple occurrences of a particular AE is only counted once within a row.

A patient with different AEs is counted in each corresponding row.

AEs (SAEs) are considered up to 7 (30) days after last study medication.

MedDRA system organ classes are listed by frequency.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Number (%) of patients reporting AEs (≥10% in any group) by system organ class and preferred term (Safety analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Total number of patients with AEs	76 (98.7)	73 (100.0)	75 (100.0)	72 (98.6)
Total number of patients with SAEs	39 (50.6)	51 (69.9)	48 (64.0)	49 (67.1)
Gastrointestinal disorders	63 (81.8)	57 (78.1)	62 (82.7)	56 (76.7)
Diarrhoea	29 (37.7)	32 (43.8)	40 (53.3)	32 (43.8)
Constipation	29 (37.7)	29 (39.7)	36 (48.0)	21 (28.8)
Nausea	22 (28.6)	29 (39.7)	36 (48.0)	20 (27.4)
Vomiting	14 (18.2)	26 (35.6)	28 (37.3)	16 (21.9)
Abdominal pain	11 (14.3)	11 (15.1)	5 (6.7)	7 (9.6)
Abdominal pain upper	9 (11.7)	5 (6.8)	4 (5.3)	3 (4.1)
Infections and infestations	48 (62.3)	55 (75.3)	59 (78.7)	50 (68.5)
Urinary tract infection	22 (28.6)	28 (38.4)	24 (32.0)	18 (24.7)
Nasopharyngitis	13 (16.9)	7 (9.6)	8 (10.7)	10 (13.7)
Upper respiratory tract infection	8 (10.4)	6 (8.2)	7 (9.3)	14 (19.2)
Metabolism and nutrition disorders	54 (70.1)	55 (75.3)	44 (58.7)	49 (67.1)
Hyperkalaemia	18 (23.4)	16 (21.9)	10 (13.3)	9 (12.3)
Diabetes mellitus	10 (13.0)	11 (15.1)	5 (6.7)	13 (17.8)
Hypophosphataemia	10 (13.0)	4 (5.5)	13 (17.3)	8 (11.0)
Hypokalaemia	8 (10.4)	2 (2.7)	10 (13.3)	12 (16.4)
Hypomagnesaemia	12 (15.6)	5 (6.8)	7 (9.3)	7 (9.6)
Hyperglycaemia	10 (13.0)	9 (12.3)	5 (6.7)	5 (6.8)
Hypocalcaemia	6 (7.8)	10 (13.7)	7 (9.3)	5 (6.8)
Injury, poisoning and procedural complications	39 (50.6)	35 (47.9)	52 (69.3)	40 (54.8)
Procedural pain	18 (23.4)	10 (13.7)	17 (22.7)	14 (19.2)
Delayed engraftment	5 (6.5)	10 (13.7)	10 (13.3)	9 (12.3)
Wound complication	9 (11.7)	7 (9.6)	10 (13.3)	7 (9.6)
Investigations	35 (45.5)	35 (47.9)	33 (44.0)	34 (46.6)
Blood creatinine increased	16 (20.8)	18 (24.7)	9 (12.0)	14 (19.2)
General disorders and administration site conditions	36 (46.8)	36 (49.3)	31 (41.3)	31 (42.5)
Oedema peripheral	20 (26.0)	21 (28.8)	17 (22.7)	13 (17.8)
Pyrexia	5 (6.5)	5 (6.8)	10 (13.3)	6 (8.2)
Renal and urinary disorders	31 (40.3)	37 (50.7)	29 (38.7)	32 (43.8)
Haematuria	9 (11.7)	4 (5.5)	9 (12.0)	11 (15.1)
Vascular disorders	31 (40.3)	38 (52.1)	28 (37.3)	29 (39.7)
Hypertension	18 (23.4)	20 (27.4)	19 (25.3)	16 (21.9)
Hypotension	4 (5.2)	11 (15.1)	5 (6.7)	6 (8.2)
Nervous system disorders	35 (45.5)	34 (46.6)	27 (36.0)	29 (39.7)

Headache	15 (19.5)	14 (19.2)	13 (17.3)	11 (15.1)
Tremor	10 (13.0)	12 (16.4)	8 (10.7)	10 (13.7)
Dizziness	6 (7.8)	5 (6.8)	4 (5.3)	8 (11.0)
Blood and lymphatic system disorders	17 (22.1)	28 (38.4)	38 (50.7)	31 (42.5)
Anaemia	9 (11.7)	11 (15.1)	25 (33.3)	12 (16.4)
Leukopenia	2 (2.6)	4 (5.5)	1 (1.3)	12 (16.4)
Skin and subcutaneous tissue disorders	31 (40.3)	23 (31.5)	29 (38.7)	27 (37.0)
Pruritus	9 (11.7)	8 (11.0)	4 (5.3)	8 (11.0)
Rash	4 (5.2)	5 (6.8)	11 (14.7)	3 (4.1)
Alopecia	8 (10.4)	3 (4.1)	8 (10.7)	3 (4.1)
Musculoskeletal and connective tissue disorders	25 (32.5)	26 (35.6)	24 (32.0)	25 (34.2)
Back pain	7 (9.1)	8 (11.0)	5 (6.7)	7 (9.6)
Pain in extremity	4 (5.2)	6 (8.2)	3 (4.0)	9 (12.3)
Respiratory, thoracic and mediastinal disorders	16 (20.8)	24 (32.9)	25 (33.3)	26 (35.6)
Cough	4 (5.2)	5 (6.8)	7 (9.3)	12 (16.4)
Dyspnoea	3 (3.9)	5 (6.8)	7 (9.3)	11 (15.1)
Psychiatric disorders	20 (26.0)	18 (24.7)	24 (32.0)	23 (31.5)
Insomnia	10 (13.0)	8 (11.0)	13 (17.3)	11 (15.1)
Cardiac disorders	11 (14.3)	24 (32.9)	22 (29.3)	15 (20.5)
Tachycardia	4 (5.2)	10 (13.7)	11 (14.7)	3 (4.1)

A patient with multiple occurrences of a particular AE is only counted once within a row.
A patient with different AEs is counted in each corresponding row.
AEs (SAEs) are considered up to 7 (30) days after last study medication.
MedDRA system organ classes and preferred terms are listed by frequency.

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations - n (%) of patients (Safety analysis set)

	AEB 100 mg + TAC SE N=77	AEB 200 mg + TAC SE N=73	AEB 300 mg + TAC RE N=75	MPA 720 mg + TAC SE N=73
Death	1 (1.3)	6 (8.2)	1 (1.3)	0
SAE(s)	39 (50.6)	51 (69.9)	48 (64.0)	49 (67.1)
Clinically significant AE(s)				
- Discontinued study medication due to AE(s)	9 (11.7)	20 (27.4)	27 (36.0)	22 (30.1)
- Dose reduction/interruption due to AE(s)	16 (20.8)	20 (27.4)	21 (28.0)	30 (41.1)

Estimated GFR using MDRD formula by visit window (Safety analysis set)

	AEB 100 mg + TAC SE N=77				MPA 720 mg + TAC SE N=73				AEB - MPA
eGFR Visit window	N	Mean	SD	Median	N	Mean	SD	Median	p-value
Day 4	70	39.0	30.20	34.4	72	32.0	24.33	29.2	0.227
Week 1	72	45.1	28.59	45.0	70	42.1	26.13	39.6	0.564
Week 2	67	53.4	23.20	53.4	65	51.3	23.14	50.4	0.582
Week 3	69	55.0	20.41	56.3	63	56.3	21.89	52.6	0.942
Month 1	69	55.9	18.60	55.2	62	58.6	21.22	54.7	0.828
Month 2	67	58.6	19.41	58.4	63	58.0	22.97	55.1	0.584
Month 3	67	56.4	17.36	54.9	64	58.6	22.29	56.7	0.994
Month 4	62	58.0	19.83	55.1	59	61.8	23.61	58.4	0.398
Month 5	60	59.4	19.66	56.7	56	62.5	24.24	58.9	0.749
Month 6	68	57.4	18.62	56.4	68	70.6	99.92	59.0	0.718
Month 9	66	59.7	21.36	57.8	63	61.0	24.72	61.1	0.884
Month 12	66	59.1	20.37	56.4	62	62.8	26.42	59.2	0.600
Month 15	66	60.6	20.86	59.6	62	62.0	22.33	61.6	0.647
Month 18	54	59.4	20.67	61.8	61	62.2	22.07	60.4	0.577
Month 21	27	58.9	22.01	54.9	39	63.7	24.87	62.8	0.506
Month 24	13	64.2	16.16	65.7	12	63.3	23.60	61.1	0.532
Month 30	2	73.5	0.49	73.5					

	AEB 200 mg + TAC SE N=73				MPA 720 mg + TAC SE N=73				AEB - MPA
eGFR Visit window	N	Mean	SD	Median	N	Mean	SD	Median	p-value
Day 4	71	29.8	22.89	27.1	72	32.0	24.33	29.2	0.505
Week 1	70	39.8	25.08	39.2	70	42.1	26.13	39.6	0.669

Week 2	69	47.0	22.81	43.4	65	51.3	23.14	50.4	0.247
Week 3	62	49.4	20.66	46.9	63	56.3	21.89	52.6	0.083
Month 1	65	49.0	19.19	47.2	62	58.6	21.22	54.7	0.023
Month 2	62	50.8	17.94	47.5	63	58.0	22.97	55.1	0.109
Month 3	61	51.2	19.09	48.4	64	58.6	22.29	56.7	0.081
Month 4	60	51.9	16.59	51.5	59	61.8	23.61	58.4	0.023
Month 5	57	51.4	16.60	49.5	56	62.5	24.24	58.9	0.009
Month 6	63	50.2	18.33	46.4	68	70.6	99.92	59.0	0.009
Month 9	64	51.8	16.77	52.6	63	61.0	24.72	61.1	0.033
Month 12	62	54.8	16.19	53.3	62	62.8	26.42	59.2	0.138
Month 15	57	55.9	17.70	51.7	62	62.0	22.33	61.6	0.100
Month 18	55	54.9	18.51	54.4	61	62.2	22.07	60.4	0.091
Month 21	40	57.2	17.98	55.5	39	63.7	24.87	62.8	0.322
Month 24	10	58.5	17.22	64.5	12	63.3	23.60	61.1	0.974

	AEB 300 mg + TAC SE N=75				**MPA 720 mg + TAC SE N=73**				**AEB + MPA**
eGFR Visit window	**N**	**Mean**	**SD**	**Median**	**N**	**Mean**	**SD**	**Median**	**p-value**
Day 4	70	35.9	28.02	27.4	72	32.0	24.33	29.2	0.543
Week 1	71	47.3	29.08	44.7	70	42.1	26.13	39.6	0.359
Week 2	68	54.2	23.70	53.6	65	51.3	23.14	50.4	0.504
Week 3	63	59.3	20.46	58.1	63	56.3	21.89	52.6	0.338
Month 1	64	62.1	20.31	58.6	62	58.6	21.22	54.7	0.173
Month 2	59	66.0	19.33	65.9	63	58.0	22.97	55.1	0.007
Month 3	64	63.0	17.90	59.8	64	58.6	22.29	56.7	0.085
Month 4	54	64.7	16.82	62.0	59	61.8	23.61	58.4	0.227
Month 5	54	63.2	18.30	62.7	56	62.5	24.24	58.9	0.384
Month 6	61	63.1	17.28	63.9	68	70.6	99.92	59.0	0.118
Month 9	60	63.4	20.15	64.0	63	61.0	24.72	61.1	0.384
Month 12	60	64.3	17.18	65.1	62	62.8	26.42	59.2	0.176
Month 15	57	62.0	18.29	62.8	62	62.0	22.33	61.6	0.875
Month 18	57	61.2	19.14	61.0	61	62.2	22.07	60.4	0.968
Month 21	33	66.1	19.24	62.3	39	63.7	24.87	62.8	0.509
Month 24	11	64.6	21.30	72.3	12	63.3	23.60	61.1	0.442
Month 30	2	81.9	16.62	81.9					

P-values are based on Wilcoxon rank sum test.

Other Relevant Findings

Increased risk of late acute rejections (lack of efficacy) in the AEB 100 mg arm.

NOVARTIS

Clinical Trial Results Database

Date of Clinical Trial Report 23-Apr-2013
Date Inclusion on Novartis Clinical Trial Results Database 4-Oct-2013
Date of Latest Update 29-May-2013