Novartis CTRD Results Template

Sponsor

Novartis

Generic Drug Name

Sotrastaurin acetate (AEB071)

Therapeutic Area of Trial

Renal transplantation

Approved Indication

Investigational

Protocol Number

CAEB071A2206

Title

A 12-month open-label, randomized, multicenter, sequential cohort, dose finding study to evaluate the efficacy, safety and tolerability of oral AEB071 versus cyclosporine in combination with everolimus, basiliximab and corticosteroids in *de novo* adult renal transplant recipients

Phase of Development

IIa/IIb

Study Start/End Dates

18 Sep 2007 to 27 Apr 2011

Study Design/Methodology

This was a 12-month, randomized, multicenter, open-label, sequential cohort, dose finding study conducted in two stages (Stage 1 = Phase IIa, assessment of efficacy and Stage 2 = Phase IIb, dose finding).
The recruitment period was in three steps. Stage 1 started with a pilot phase enrolling 45 patients at selected sites into two arms (2:1 AEB071 300 mg and control). An interim analysis of key safety and efficacy data of these patients was deemed satisfactory by the Data Monitoring Committee and, therefore, enrollment into the remainder of Stage 1 continued at all study sites. Once all the patients of Stage 1 had been randomized (2:1 randomization), the trial stopped enrollment. A total of 131 patients were enrolled in the 2 arms, 2:1 (85 patients in the AEB071 300 mg bid arm and 46 patients in the control arm). When all Stage 1 patients had reached 3 months treatment time, a second interim analysis of efficacy and safety variables was performed and an additional treatment arm with a dose of 200 mg bid was selected for Stage 2. A total of 180 patients were randomized 1:1:1 to the three treatment arms in stage 2 (actual randomization: 63 patients in the AEB071 200 mg bid arm, 55 patients in the AEB071 300 mg bid arm, and 62 patients in the control arm).
All patients enrolled in Stage 1 or Stage 2, were treated for 12 months at their randomized dose of AEB071 or cyclosporine.

Centres

Stage 1 - 17 centers in 12 countries: Argentina (1), Belgium (1), Brazil (1), Czech Republic (1), Netherlands (1), Norway (1), Switzerland (1), Taiwan (1), Australia (2), Austria (2), France (2), Italy (3)
Stage 2 - 27 centers in 17 countries: Austria (1), Czech Republic (1), Italy (1), Netherlands (1), Norway (1), Poland (1), Singapore (1), Switzerland (1), Taiwan (1), Argentina (2), Brazil (2), Colombia (2), Germany (2), Slovakia (2), Spain (2), Australia (3), France (3)

Publication

None

Outcome measures

Primary outcome measures(s)

Occurrence of efficacy failure, defined as treated BPAR (tBPAR) of grade 1A or higher, graft loss, death, or loss to follow-up.

Secondary outcome measures(s)

- Occurrence of treated biopsy-proven acute rejections, graft loss, or death
- Occurrence of treated acute rejections, graft loss, death, or lost to follow-up
- Occurrence of sub-clinical rejection, treated biopsy-proven acute rejection, or treated acute rejections
- Occurrence of treated biopsy-proven acute rejection
- Occurrence of biopsy-proven acute rejection (BPAR)
- Occurrence of treated acute rejections (tAR)
- Occurrence of chronic allograft nephropathy (CAN)
- Occurrence of graft loss, death, or lost to follow-up
- Occurrence of graft loss or death
- Occurrence of graft loss
- Occurrence of death
- Occurrence of lost to follow-up (LTFU)
- Calculated glomerular filtration rate (GFR) at Month 3, 6, and 12 for Stage 1 and Stage 2 using the MDRD formula

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

Test product: Oral hard gelatin capsules of AEB071, either 200 mg bid or 300 mg bid

Reference product: Oral cyclosporine according to local availability (blistered or bottles), 4-8 mg/kg/day

Starting dose of cyclosporine within 24 h of graft reperfusion	Month 1 Day 2 to 29 (ng/mL)	Month 2-3 Day 30 to 119 (ng/mL)	Month 4-5 Day 120 to 179 (ng/mL)	Month 6-12 Day 180 to 360 (ng/mL)
4-8 mg/kg/day	100-200	75-150	50-100	25-50

Everolimus, basiliximab and steroids were commercially available in the participating countries and was purchased according to local availability (blistered or bottles) and labeled according to local requirements.
Dose and target trough level ranges of everolimus:

Treatment arm	Starting dose of everolimus within 24 h of graft reperfusion	Week 1-2 Day 2 - 14 (ng/mL)	Week 3 to Month 12 Day 15 - 360 (ng/mL)
Control	3 mg/day	4-8	4-8
AEB071 300 mg bid	6 mg/day	4-8	4-8
AEB071 200 mg bid	6 mg/day	4-8	8-12

Statistical Methods

Due to the exploratory nature of this study (i.e. modest sample sizes and uncertainty in expected event rates at different doses of AEB071), there was no formal hypothesis testing performed. Instead, an estimation approach was used. Sample sizes were chosen to ensure sufficient evidence of non-inferiority between event rates in an AEB071 arm and control arm. A 20% non-inferiority margin, while larger than typically used in Phase III confirmatory trials, was selected as a guideline for determining doses for Stage 2.

The primary efficacy variable was the occurrence of efficacy failure, defined as treated biopsy proven acute rejection of grade 1A or higher, graft loss, death, or lost to follow-up. The acute rejection rating obtained from the local pathologist's assessment was used in the primary analysis.

The primary efficacy analysis used Kaplan-Meier (KM) methodology to estimate event rates for intent-to-treat (ITT) population. 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 time point for the analysis was Month 3 (Day 90) for Stage 1 and Month 6 (Day 180) for Stage 2. For the Kaplan-Meier estimate at Month 12, the estimate at Day 360 from the Kaplan-Meier table was used. The censor day for patients without an event was last contact day.

The secondary efficacy variables were analyzed as the primary efficacy variable for Month 3 (Day 90), Month 6 (Day 180) and Month 12 (Day 360). A summary of the Kaplan-Meier estimates and the Kaplan-Meier figure was given for the tBPAR only.

Additionally frequency tables were provided for the maximum severity of the Banff score and the occurrence of antibody-mediated rejections (local and central pathologists' assessment, all data and on-treatment) as well as how the acute rejections were treated. The number of acute rejection episodes per patient were tabulated (all data and on-treatment).

The primary safety variable was the calculated GFR at Month 3, 6, and 12 for Stage 1 and Stage 2 using the MDRD formula. Descriptive statistics for calculated GFR by visit window were calculated. The values were compared between treatment groups using the Wilcoxon Rank Sum test supported by the 95% confidence interval for the location shift between AEB071 groups and the control group (Hodges-Lehman estimator) with on-treatment values as well as all available data. A boxplot of GFR by visit window was displayed.

Other safety parameters were summarized using incidence tables and descriptive statistics. AEs (including infections) were coded by MedDRA and summarized by primary system organ class, preferred term, severity and study drug relationship. Infections were also coded by SNOMED and summarized by type of infection and specific micro-organism.

The preferred terms "Nausea", "Vomiting", "Diarrhea", "Constipation", "Dysgeusia", "Tachycardia" and "Sinus tachycardia" were of special interest. All selected preferred terms were analyzed with regard to the following variables: seriousness, maximum severity, relationship with study drug, action taken, total duration, number of occurrences of AEs, and time to the day of AE onset. Furthermore, the time to the first AE onset was analyzed using Kaplan-Meier estimates.

Signs and symptoms specific for calcineurin inhibitors (tremor, muscular/skeletal pain, hypertrichosis, gingival hyperplasia) were summarized. The number and percentage of patients who had an event were tabulated by visit window.

A multifactorial analysis was performed to explain the difference in the efficacy failure rate between the two stages. The factors used were “donor recipient gender match (yes/no)”, “panel reactive antibodies (≤5% vs. >5%)” and “donor age (≤50years vs. >50 years)”.

Study Population: Inclusion/Exclusion Criteria and Demographics

Eligible patients were male or female renal recipients ≥18 years old undergoing primary transplantation who provided written informed consent and met the following key inclusion criteria:

1. Deceased, living unrelated or non-HLA identical living related donor 10-65 years old
2. Cold ischemia time < 24 h.
3. Functional graft within 24 h after graft reperfusion
4. Ability to take oral medication within 24 h after graft reperfusion.

The key exclusion criteria were:

1. Multi-organ transplant recipients or if the patient previously received an organ transplant or recipients of an organ from a non-heart beating donor.
2. Receipt of A-B-O incompatible transplants, all CDC cross-match positive transplants.
3. Patients who are treated with drugs that are strong inducers or inhibitors of CYP3A4 at screening and who cannot discontinue this treatment
4. QTcF > 500 ms, long QT syndrome or with a family history of sudden unexplained death.
5. Patients with left bundle branch block or who experienced, during the previous 6 months, hospitalization for heart failure of cardiac etiology, or significant and persistent left-ventricular dysfunction (ejection fraction < 40%).
6. History, in the preceding 3 months, of significant and persistent arrhythmias such as ventricular fibrillation or tachycardia, or atrial fibrillation or flutter or requirement of antiarrhythmic drugs with QT-prolonging properties.
7. Symptomatic coronary artery disease.
8. Sensitized patients (most recent anti-HLA class I Panel Reactive Antibodies (PRA) > 20% by a CDC-based assay or > 50% by a flow cytometry or ELISA-based assay) or patients identified otherwise to be at high immunological risk.
9. History of malignancy of any organ system, treated or untreated, within the past 5 years regardless of evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin (excised ≥ 2 years prior to randomization).
10. Pregnant or nursing (lactating) women and women who might become pregnant during the study

Participant Flow

Patient disposition for Stage 1 (ITT analysis set)

	cyclosporine + everolimus n (%) N = 46	AEB 300mg bid + everolimus n (%) N = 85
Study medication completion		
Continued study medication at Month 12	31 (67.4)	50 (58.8)
Discontinued study medication prior to Month 12	15 (32.6)	35 (41.2)
Main reason for discontinuation of the study medication		
Administrative problems	0	1 (1.2)
Adverse Event(s)	13 (28.3)	18 (21.2)
Death	0	2 (2.4)
Protocol violation	0	1 (1.2)
Subject withdrew consent	1 (2.2)	1 (1.2)
Unsatisfactory therapeutic effect	1 (2.2)	12 (14.1)
Study completion		
Completed study at Month 12	44 (95.7)	81 (95.3)
Discontinued study prior to Month 12	2 (4.4)	4 (4.7)
Main reason for discontinuation of the study (withdrawal)		
Death	0	3 (3.5)
Lost to follow-up	1 (2.2)	1 (1.2)
Subject withdrew consent	1 (2.2)	0

Patient disposition for Stage 2 (ITT analysis set)

	cyclosporine + everolimus n (%) N = 62	AEB 200mg bid + everolimus n (%) N = 63	AEB 300mg bid + everolimus n (%) N = 55
Study medication completion			
Continued study medication at Month 12	41 (66.1)	41 (65.1)	27 (49.1)
Discontinued study medication prior to Month 12	21 (33.9)	22 (34.9)	28 (50.9)
Main reason for discontinuation of the study medication			
Administrative problems	1 (1.6)	0	0
Adverse Event(s)	10 (16.1)	13 (20.6)	18 (32.7)
Death	0	0	1 (1.8)
Graft loss	0	1 (1.6)	0
Protocol violation	2 (3.2)	0	0
Subject withdrew consent	1 (1.6)	1 (1.6)	1 (1.8)
Unsatisfactory therapeutic effect	7 (11.3)	7 (11.1)	8 (14.6)
Study completion			
Completed study at Month 12	60 (96.8)	61 (96.8)	47 (85.5)
Discontinued study prior to Month 12	2 (3.2)	2 (3.2)	8 (14.6)
Main reason for discontinuation of the study (withdrawal)			
Administrative problems	1 (1.6)	1 (1.6)	0
Death	0	0	4 (7.3)
Lost to follow-up	1 (1.6)	1 (1.6)	2 (3.6)
Subject withdrew consent	0	0	2 (3.6)

Baseline Characteristics

Recipient demographic and disease characteristics summary for Stage 1 (ITT analysis set)

		cyclosporine + everolimus N=46	AEB 300mg bid + everolimus N=85
Age (years)	N	46	85
	Mean	43.2	45.8
	SD	11.02	13.87
	Median	44.0	47.0
	Range	20, 65	19, 70
Age group - n (%)	< 65	45 (97.8)	81 (95.3)
	≥ 65	1 (2.2)	4 (4.7)
Gender - n (%)	Male from male donor	16 (34.8)	25 (29.4)
	Male from female donor	16 (34.8)	28 (32.9)
	Female from male donor	7 (5.2)	16 (18.8)
	Female from female donor	7 (15.2)	16 (18.8)
Race - n (%)	Asian	1 (2.2)	0
	Black	1 (2.2)	5 (5.9)
	Caucasian	39 (84.8)	74 (87.1)
	Other	4 (8.7)	6 (7.1)
	Unknown	1 (2.2)	0
End Stage Disease Leading to Transplantation - n (%)	Glomerulonephritis / glomerular disease	9 (19.6)	19 (22.4)
	Pyelonephritis	2 (4.3)	4 (4.7)
	Polycystic disease	7 (15.2)	16 (18.8)
	Hypertension / nephrosclerosis	6 (13.0)	5 (5.9)
	Diabetes mellitus	3 (6.5)	4 (4.7)
	Interstitial nephritis	0	1 (1.2)
	Obstructive disorder / reflux	3 (6.5)	2 (2.4)
	Renal hyperplasia / dysplasia	0	1 (1.2)
	Unknown	10 (21.7)	21 (24.7)
	Other	6 (13.0)	12 (14.1)
Pre-Op status - n (%)	None	10 (21.7)	23 (27.1)
	Hemodialysis	27 (58.7)	54 (63.5)
	Peritoneal dialysis	9 (19.6)	8 (9.4)
Panel Reactive Antibodies - Most Recent Evaluation (%)	N	46	85
	Mean	0.8	1.0
	SD	3.78	3.35
	Median	0	0
	Range	0, 24.0	0, 25.0
Cold Ischemia Time (h)	N	18	28
	Mean	14.9	14.6
	SD	5.57	4.24
	Median	15.9	15.1
	Range	4.0, 23.0	8.0, 23.7

Recipient demographic and disease characteristics summary for Stage 2 (ITT analysis set)

		cyclosporine + everolimus N=62	AEB 200mg bid + everolimus N=63	AEB 300mg bid + everolimus N=55
Age (years)	N	62	63	55
	Mean	45.0	45.5	44.3
	SD	11.81	13.67	13.62
	Median	46.5	48.0	46.0
	Range	18, 66	19, 69	20, 69
Age group - n (%)	< 65	61 (98.4)	59 (93.7)	53 (96.4)
	≥ 65	1 (1.6)	4 (6.4)	2 (3.6)
Gender - n (%)	Male from male donor	25 (40.3)	19 (30.2)	15 (27.3)
	Male from female donor	17 (27.4)	20 (31.8)	21 (38.2)
	Female from male donor	13 (21.0)	13 (20.6)	12 (21.8)
	Female from female donor	7 (11.3)	11 (17.5)	7 (12.7)
Race - n (%)	Asian	1 (1.6)	2 (3.2)	1 (1.8)
	Black	2 (3.2)	1 (1.6)	5 (9.1)
	Caucasian	47 (75.8)	47 (74.6)	36 (65.5)
	Missing	1 (1.6)	1 (1.6)	0
	Other	11 (17.7)	12 (19.1)	13 (23.6)
End Stage Disease Leading to Transplantation - n (%)	Glomerulonephritis / glomerular disease	13 (21.0)	11 (17.5)	9 (16.4)
	Pyelonephritis	1 (1.6)	1 (1.6)	1 (1.8)
	Polycystic disease	10 (16.1)	13 (20.6)	9 (16.4)
	Hypertension / nephrosclerosis	10 (16.1)	5 (7.9)	11 (20.0)
	Drug induced toxicity	1 (1.6)	0	0
	Diabetes mellitus	6 (9.7)	4 (6.4)	4 (7.3)
	Interstitial nephritis	2 (3.2)	4 (6.4)	1 (1.8)
	Obstructive disorder / reflux	1 (1.6)	5 (7.9)	2 (3.6)
	Unknown	11 (17.7)	13 (20.6)	13 (23.6)
	Other	7 (11.3)	7 (11.1)	5 (9.1)
Pre-Op status - n (%)	None	13 (21.0)	13 (20.6)	10 (18.2)
	Hemodialysis	41 (66.1)	42 (66.7)	39 (70.9)
	Peritoneal dialysis	8 (12.9)	8 (12.7)	6 (10.9)
Panel Reactive Antibodies - Most Recent Evaluation (%)	N	62	63	55
	Mean	0.9	0.9	1.6
	SD	3.76	3.38	5.41
	Median	0	0	0
	Range	0, 27.0	0, 24.0	0, 38.0
Cold Ischemia Time (h)	N	31	31	27
	Mean	15.0	16.0	16.7
	SD	5.30	4.99	4.22
	Median	15.8	16.3	15.6
	Range	5.7, 23.5	5.0, 23.7	10.1, 23.4

Donor characteristics for Stage 1 (ITT analysis set)

		cyclosporine + everolimus N = 46	AEB 300mg bid + everolimus N = 85
Donor age (years)	N	46	85
	Mean	45.8	42.9
	SD	12.68	12.37
	Median	48.0	44.0
	Range	17, 65	16, 64
Donor characteristic – n (%)	Living related	21 (45.7)	36 (42.4)
	Living unrelated	7 (15.2)	21 (24.7)
	Deceased heart beating	18 (39.1)	28 (32.9)

Donor characteristics for Stage 2 (ITT analysis set)

		cyclosporine + everolimus N= 62	AEB 200mg bid + everolimus N= 63	AEB 300mg bid + everolimus N= 55
Donor age (years)	N	62	63	55
	Mean	43.4	42.4	41.0
	SD	12.14	14.06	11.96
	Median	45.0	45.0	42.0
	Range	15, 61	12, 69	19, 65
Donor characteristic – n (%)	Living related	24 (38.7)	23 (36.5)	17 (30.9)
	Living unrelated	7 (11.3)	9 (14.3)	11 (20.0)
	Deceased heart beating	31 (50.0)	31 (49.2)	27 (49.1)

Outcome measures

Primary Outcome Result(s)

Analysis of the primary efficacy failure event in Stage 1 at Month 3 (ITT analysis set)

	cyclosporine + everolimus N=46	AEB 300mg bid + everolimus N=85	Difference to control: AEB 300mg bid - cyclosporine
Composite efficacy failure (Month 3)			
Number of events	4	7	
K-M failure rate (%)	8.7	8.2	-0.5
95% CI (%)	(0.6, 16.8)	(2.4, 14.1)	(-10.5,9.6)
Treated BPAR (Month 3)			
Number of events	3	5	
K-M failure rate (%)	6.5	6.0	-0.6
95% CI (%)	(0.0, 13.7)	(0.9, 11.0)	(-9.3,8.2)

Composite efficacy failure: Treated BPAR, graft loss, death, or lost to follow-up. K-M = Kaplan-Meier, negative differences favor AEB071.

One patient from Stage 1 randomized to control arm was treated with AEB071 throughout the study and experienced a treated BPAR on Day 40.

Analysis of the primary efficacy failure event in Stage 2 at Month 6 (ITT analysis set)

				Difference to control	
	cyclosporine + everolimus N=62	AEB 200mg bid + everolimus N=63	AEB 300mg bid + everolimus N=55	AEB 200mg bid - cyclosporine	AEB 300mg bid - cyclosporine

Composite efficacy failure (Month 6)					
Number of events	10	13	17		
K-M failure rate (%)	16.1	20.7	30.9	4.5	14.8
95% CI (%)	(7.0, 25.3)	(10.7, 30.7)	(18.7, 43.1)	(-9.0,18.1)	(-0.5,30.0)
Treated BPAR (Month 6)					
Number of events	10	12	14		
K-M failure rate (%)	16.1	19.1	26.0	2.9	9.9
95% CI (%)	(7.0, 25.3)	(9.4, 28.8)	(14.3, 37.8)	(-10.4,16.3)	(-5.0,24.8)

Composite efficacy failure: Treated BPAR, graft loss, death, or lost to follow-up. K-M = Kaplan-Meier, negative differences favor AEB071.

Secondary Outcome Result(s)

Comparison of Kaplan-Meier estimates of first efficacy event, AEB 300mg bid regimen vs control (ITT Analysis set): Stage 1, Month 12

	cyclosporine + everolimus N=46		AEB 300mg bid + everolimus N=85		Difference in KM estimate (AEB 300mg bid – cyclosporine)	p-value	
	Number with event	KM estimate (SE)	Number with event	KM estimate (SE)	Difference (95% CI) (%)	Difference in KM estimate	Log-Rank
tBPAR, graft loss, death, LTFU	5	10.9 (4.59)	14	16.5 (4.02)	5.6 (-6.4, 17.6)	0.359	0.400
tBPAR, graft loss, death	3	6.5 (3.64)	14	16.5 (4.02)	9.9 (-0.7, 20.6)	0.067	0.124
tAR, graft loss, death, LTFU	5	10.9 (4.59)	16	18.8 (4.24)	8.0 (-4.3, 20.2)	0.203	0.255
sub-clinical rej, tBPAR, tAR	3	6.5 (3.64)	13	15.6 (3.98)	9.1 (-1.5, 19.7)	0.091	0.158
tBPAR	3	6.5 (3.64)	11	13.2 (3.71)	6.7 (-3.5, 16.9)	0.199	0.271
BPAR	3	6.5 (3.64)	12	14.4 (3.85)	7.9 (-2.5, 18.3)	0.137	0.207
tAR	3	6.5 (3.64)	13	15.6 (3.98)	9.1 (-1.5, 19.7)	0.091	0.157
CAN	2	4.4 (3.08)	8	9.8 (3.29)	5.4 (-3.5, 14.2)	0.234	0.322
Graft loss, death, LTFU	2	4.3 (3.01)	4	4.7 (2.30)	0.4 (-7.1, 7.8)	0.925	0.926
Graft loss, death	0	0	4	4.7 (2.30)	4.7 (0.2, 9.2)	0.040	0.142
Graft loss	0	0	1	1.2 (1.21)	1.2 (-1.2, 3.6)	0.314	0.464
Death	0	0	3	3.5 (2.00)	3.5 (-0.4, 7.5)	0.078	0.203
LTFU	2	4.3 (3.01)	1	1.2 (1.21)	-3.1 (-9.5, 3.2)	0.335	0.255

Comparison of Kaplan-Meier estimates of first efficacy event, AEB 300mg bid regimen vs control (ITT Analysis set): Stage 2, Month 12

	cyclosporine + everolimus N=62		AEB 300mg bid + everolimus N=55		Difference in KM estimate (AEB 300mg bid – cyclosporine)	p-value	
	Number with event	KM estimate (SE)	Number with event	KM estimate (SE)	Difference (95% CI) (%)	Difference in KM estimate	Log-Rank
tBPAR, graft loss, death,	12	19.4 (5.02)	19	34.5 (6.41)	15.2 (-0.8, 31.1)	0.062	0.073

LTFU							
tBPAR, graft loss, death	12	19.4 (5.02)	17	31.2 (6.28)	11.8 (-3.9, 27.6)	0.141	0.152
tAR, graft loss, death, LTFU	14	22.6 (5.31)	20	36.4 (6.49)	13.8 (-2.6, 30.2)	0.100	0.108
sub-clinical rej, tBPAR, tAR	14	22.6 (5.31)	16	29.8 (6.27)	7.2 (-8.9, 23.4)	0.378	0.373
tBPAR	12	19.4 (5.02)	15	28.0 (6.15)	8.6 (-6.9, 24.2)	0.277	0.290
BPAR	13	21.0 (5.17)	15	27.9 (6.13)	6.9 (-8.8, 22.6)	0.389	0.385
tAR	14	22.6 (5.31)	16	29.8 (6.27)	7.2 (-8.9, 23.4)	0.378	0.373
CAN	5	8.1 (3.49)	5	9.7 (4.13)	1.5 (-9.1, 12.1)	0.775	0.730
Graft loss, death, LTFU	1	1.6 (1.60)	9	16.4 (4.99)	14.8 (4.5, 25.0)	0.005	0.004
Graft loss, death	0	0	7	12.9 (4.56)	12.9 (4.0, 21.8)	0.005	0.004
Graft loss	0	0	3	5.7 (3.22)	5.7 (-0.6, 12.1)	0.075	0.057
Death	0	0	4	7.6 (3.64)	7.6 (0.4, 14.7)	0.038	0.028
LTFU	1	1.6 (1.60)	4	7.6 (3.64)	5.9 (-1.8, 13.7)	0.134	0.120

Comparison of Kaplan-Meier estimates of first efficacy event, AEB 200mg bid regimen vs control (ITT Analysis set): Stage 2, Month 12

	cyclosporine + everolimus N=62		**AEB 200mg bid + everolimus N=63**		**Difference in KM estimate (AEB 200mg bid – cyclosporine)**	**p-value**	
	Number with event	**KM estimate (SE)**	**Number with event**	**KM estimate (SE)**	**Difference (95% CI) (%)**	**Difference in KM estimate**	**Log-Rank**
tBPAR, graft loss, death, LTFU	12	19.4 (5.02)	17	27.2 (5.63)	7.8 (-7.0, 22.6)	0.300	0.355
tBPAR, graft loss, death	12	19.4 (5.02)	17	27.2 (5.63)	7.8 (-7.0, 22.6)	0.300	0.355
tAR, graft loss, death, LTFU	14	22.6 (5.31)	18	28.8 (5.73)	6.2 (-9.1, 21.5)	0.426	0.497
sub-clinical rej, tBPAR,	14	22.6 (5.31)	18	28.8 (5.73)	6.2 (-9.1, 21.5)	0.426	0.486

tAR							
tBPAR	12	19.4 (5.02)	16	25.6 (5.52)	6.2 (-8.4, 20.9)	0.404	0.469
BPAR	13	21.0 (5.17)	16	25.6 (5.52)	4.6 (-10.2, 19.4)	0.541	0.607
tAR	14	22.6 (5.31)	17	27.2 (5.64)	4.6 (-10.6, 19.8)	0.550	0.632
CAN	5	8.1 (3.49)	3	4.9 (2.77)	-3.2 (-12.0, 5.5)	0.469	0.465
Graft loss, death, LTFU	1	1.6 (1.60)	2	3.2 (2.23)	1.6 (-3.8, 7.0)	0.563	0.564
Graft loss, death	0	0	2	3.2 (2.23)	3.2 (-1.2, 7.6)	0.151	0.159
Graft loss	0	0	2	3.2 (2.23)	3.2 (-1.2, 7.6)	0.151	0.159
Death	0	0	0	0	0	-	-
LTFU	1	1.6 (1.60)	1	1.6 (1.60)	0.0 (-4.4, 4.4)	1.000	0.995

Calculated GFR using MDRD formula, by visit window (Safety analysis set): Stage 1 and 2

	cyclosporine + everolimus			**AEB 200mg bid + everolimus**			**AEB 300mg bid + everolimus**			**Group difference**	
Visit Window	**N**	**Mean ± SD**	**Median**	**N**	**Mean ± SD**	**Median**	**N**	**Mean ± SD**	**Median**	**AEB 200mg bid – cyclosporine P-value**	**AEB 300mg bid – cyclosporine P-value**
Week 1	103	46.7 ± 22.13	48.0	61	53.2 ± 25.43	56.0	134	55.9 ± 25.99	54.0	0.043	0.007
Month 1	96	56.4 ± 19.51	56.0	60	63.0 ± 17.09	65.0	124	63.5 ± 21.77	62.5	0.022	0.008
Month 3	85	54.4 ± 16.89	52.0	53	63.7 ± 14.78	63.0	105	64.6 ± 19.09	63.0	<.001	<.001
Month 6	82	54.3 ± 14.73	54.5	47	60.0 ± 14.59	61.0	91	61.8 ± 20.49	60.0	0.010	0.002
Month 12	77	55.9 ± 16.28	55.0	40	59.8 ± 16.53	61.5	76	64.4 ± 17.49	60.5	0.280	0.006
SEP	105	52.2 ± 18.90	53.0	62	56.0 ± 18.34	56.0	140	58.0 ± 23.02	56.0	0.204	0.038

Calculated GFR (MDRD) “on-treatment” analysis
P-value is based on Wilcoxon's rank sum test.

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events/infections by primary system organ class and treatment group (Safety analysis set): Stage 1 and 2

Primary System Organ Class	cyclosporine + everolimus N=107	AEB 200mg bid + everolimus N=63	AEB 300mg bid + everolimus N=140
Any AE/Infection	106 (99.1)	63 (100.0)	140 (100.0)
Blood and lymphatic system disorders	45 (42.1)	20 (31.7)	51 (36.4)
Cardiac disorders	16 (15.0)	17 (27.0)	38 (27.1)
Congenital, familial and genetic disorders	1 (0.9)	0	2 (1.4)
Ear and labyrinth disorders	4 (3.7)	1 (1.6)	8 (5.7)
Endocrine disorders	8 (7.5)	2 (3.2)	4 (2.9)
Eye disorders	9 (8.4)	6 (9.5)	5 (3.6)
Gastrointestinal disorders	79 (73.8)	51 (81.0)	116 (82.9)
General disorders and administration site conditions	55 (51.4)	40 (63.5)	73 (52.1)
Hepatobiliary disorders	6 (5.6)	3 (4.8)	7 (5.0)
Immune system disorders	17 (15.9)	7 (11.1)	19 (13.6)
Infections and infestations	74 (69.2)	47 (74.6)	100 (71.4)
Injury, poisoning and procedural complications	60 (56.1)	36 (57.1)	72 (51.4)
Investigations	39 (36.4)	29 (46.0)	50 (35.7)
Metabolism and nutrition disorders	81 (75.7)	50 (79.4)	98 (70.0)
Musculoskeletal and connective tissue disorders	39 (36.4)	22 (34.9)	48 (34.3)
Neoplasms benign, malignant and unspecified	12 (11.2)	4 (6.3)	7 (5.0)
Nervous system disorders	46 (43.0)	22 (34.9)	39 (27.9)
Psychiatric disorders	25 (23.4)	10 (15.9)	23 (16.4)
Renal and urinary disorders	53 (49.5)	28 (44.4)	63 (45.0)
Reproductive system and breast disorders	15 (14.0)	6 (9.5)	17 (12.1)
Respiratory, thoracic and mediastinal disorders	18 (16.8)	21 (33.3)	25 (17.9)
Skin and tissue disorders	54 (50.5)	44 (69.8)	68 (48.6)
Surgical and medical procedures	2 (1.9)	2 (3.2)	4 (2.9)
Vascular disorders	46 (43.0)	34 (54.0)	53 (37.9)

10 Most Frequently Reported AEs Overall by Preferred Term n (%) (Safety analysis set): Stage 1 and 2

	cyclosporine + everolimus N=107	AEB 200mg bid + everolimus N=63	AEB 300mg bid + everolimus N=140
Constipation	44 (41.1)	33 (52.4)	71 (50.7)
Diarrhea	22 (20.6)	18 (28.6)	57 (40.7)
Vomiting	17 (15.9)	13 (20.6)	49 (35.0)
Urinary tract infection	33 (30.8)	21 (33.3)	47 (33.6)
Nausea	28 (26.2)	19 (30.2)	46 (32.9)
Anemia	34 (31.8)	11 (17.5)	45 (32.1)
Edema peripheral	42 (39.3)	24 (38.1)	44 (31.4)
Hypokalemia	12 (11.2)	7 (11.1)	32 (22.9)
Hypophosphatemia	19 (17.8)	14 (22.2)	25 (17.9)
Hypertension	27 (25.2)	16 (25.4)	25 (17.9)

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (Safety analysis set): Stage 1 and 2

	cyclosporine + everolimus N=107 n (%)	AEB 200mg bid + everolimus N=63 n (%)	AEB 300mg bid + everolimus N=140 n (%)
Death	0	0	6 (4.3)
SAE(s)	66 (61.7)	41 (65.1)	95 (67.9)
Clinically significant AE(s)/infection(s)	54 (50.5)	30 (47.6)	83 (59.3)
Discontinued study medication due to AE(s)	28 (26.2)	17 (27.0)	51 (36.4)
Dose reduction/interruption due to AE(s)	36 (33.6)	20 (31.7)	47 (33.6)

SAEs and deaths are considered up to 30 days after last study medication.
Clinically significant AEs are considered up to 7 days after last study medication.

Other Relevant Findings

None

Date of Clinical Trial Report

10 Apr 2012

Date Inclusion on Novartis Clinical Trial Results Database

26 Apr 2012

Date of Latest Update

Not applicable