Sponsor

Novartis

Generic Drug Name

Sotrastaurin acetate

Therapeutic Area of Trial

Renal transplant

Approved Indication

Investigational

Protocol Number

CAEB071A2206E1

Title

An extension to a 12-month, open-label, randomized, multicenter, sequential cohort, dose finding study to evaluate the efficacy, safety and tolerability of oral AEB071 versus Neoral® in combination with Certican®, Simulect® and corticosteroids in *de novo* adult renal transplant recipients.

Study Phase

Phase II

Study Start/End Dates

Study initiation date: 29-Sep-2008 (first patient first visit)

Early termination date: 27-Mar-2012

Study completion date: 30-Jul-2012 (last patient last visit)

Study Design/Methodology

This was a 12 to 48-month extension to a 12-month, open label, randomized, multicenter study evaluating efficacy, safety and tolerability of oral AEB071 plus Certican versus Neoral plus Certican in de novo renal transplant recipients.

Control patients continued on Neoral, Certican and steroids and patients receiving AEB071 in the core study continued to receive the respective dose of AEB071, Certican and steroids.

Centers

A total of 28 centers across 17 countries (one each in Austria, Belgium, Czech Republic, Netherlands, Norway, Singapore, Switzerland, Taiwan; two each in Argentina, Brazil, Colombia, Germany, Italy, Slovakia, Spain; and three each in Australia and France) were involved in the study

Publication

None

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

AEB071 100 mg hard gelatin capsules for oral administration either as_

1. Oral AEB071 300 mg bid (Arm 2)
2. Oral AEB071 200 mg bid (Arm 3)

Statistical Methods

Descriptive statistics for calculated GFR (MDRD) for the entire period by visit window was provided. The values were compared between treatment groups using the Wilcoxon Rank Sum test supported by the 95% confidence interval (CI) for the location shift between AEB071 groups and the control group (Hodges-Lehman estimator) with entire on-treatment data.

Efficacy evaluations were based on the extension ITT analysis set if not otherwise specified. Stage 1 and 2 were combined for all efficacy analyses.

The efficacy variable was the occurrence of composite efficacy failure. The efficacy analysis used Kaplan-Meier methodology to estimate event rates. Greenwood's formula was used to estimate standard errors and to derive the asymptotic two-sided 95% CI from the Z-test statistic distribution for the difference in event rates between the AEB071 and control arms.

The composite endpoint analyzed using log-rank test supported the efficacy analyses. Additionally frequency tables were provided for the maximum severity of the Banff score and the occurrence of antibody-mediated rejections for the entire period (local and central pathologists' assessment). The number of acute rejection episodes per patient for the entire period was tabulated.

Other safety parameters were summarized using incidence tables and descriptive statistics. All analyses were based on the extension safety analysis set, Stage 1 and 2 were combined for the analyses. Adverse Events (AEs; including infections) were coded by MedDRA and summarized by primary system organ class, preferred term, severity and study drug relationship. The number and percentage of patients with infections, and/or serious infections for the entire period were presented by type of organism (bacterial, fungal, viral, other and unknown) and microorganism (coded with NovORG).

Standardized MedDRA queries (SMQs) were used to combine relevant preferred terms to medical entities.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

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

- The patient had given written informed consent to participate in the extension study.
- The patient had been maintained on AEB071/Certican or Neoral/Certican, consistent with their original randomization, at their core study Month 12 visit.
- Women capable of becoming pregnant were required to practice a medically approved method of birth control as long as they were on study medication and for a period of 3 months following discontinuation of study drug(s).

Exclusion criteria

- Inability or unwillingness to comply with the immunosuppressive regimen or the protocol.
- Pregnancy.

Participant Flow

Patient disposition – Extension ITT analysis set

	Neoral + Certican n (%) N = 65	AEB 200mg bid + Certican n (%) N = 38	AEB 300mg bid + Certican n (%) N = 71
Extension medication completion			
Completed the extension study medication	0	0	0
Discontinued the extension study medication	65 (100.0)	38 (100.0)	71 (100.0)
Main reason for study medication discontinuation in the extension phase			
Abnormal laboratory value(s)	1 (1.5)	0	0
Abnormal test procedure result(s)	0	0	0
Administrative problems	52 (80.0)	31 (81.6)	54 (76.1)
Adverse Event(s)	7 (10.8)	5 (13.2)	12 (16.9)
Death	1 (1.5)	0	2 (2.8)
Graft loss	0	0	0
Lost to follow-up	1 (1.5)	0	1 (1.4)
Protocol violation	1 (1.5)	0	0
Subject withdrew consent	1 (1.5)	0	2 (2.8)
Unsatisfactory therapeutic effect	1 (1.5)	2 (5.3)	0
Extension completion			
Completed the extension phase	0	0	0
Discontinued the extension phase (withdrawal)	65 (100.0)	38 (100.0)	71 (100.0)
Main reason for study discontinuation in the extension phase (withdrawal)			
Administrative problems	59 (90.8)	37 (97.4)	62 (87.3)
Death	1 (1.5)	0	4 (5.6)
Lost to follow-up	3 (4.6)	0	1 (1.4)
Subject withdrew consent	2 (3.1)	1 (2.6)	4 (5.6)

Baseline Characteristics

Recipient demographic and disease characteristics summary – Extension ITT analysis set

		Neoral + Certican N=65	AEB 200mg bid + Certican N=38	AEB 300mg bid + Certican N=71
Age (years)	n	65	38	71
	Mean	44.8	46.0	45.4
	SD	11.80	14.01	13.21

	Median	45.0	49.5	46.0
	Range	18, 66	21, 69	18, 67
Age group - n (%)	<65	63 (96.9)	35 (92.1)	69 (97.2)
	>=65	2 (3.1)	3 (7.9)	2 (2.8)
Gender - n (%)	Male from Male donor	26 (40.0)	12 (31.6)	20 (28.2)
	Male from Female donor	19 (29.2)	13 (34.2)	21 (29.6)
	Female from Male donor	10 (15.4)	8 (21.1)	17 (23.9)
	Female from Female donor	10 (15.4)	5 (13.2)	13 (18.3)
Race - n (%)	Asian	1 (1.5)	1 (2.6)	0
	Black	2 (3.1)	1 (2.6)	6 (8.5)
	Caucasian	53 (81.5)	29 (76.3)	56 (78.9)
	Missing	0	1 (2.6)	0
	Other	9 (13.9)	6 (15.8)	9 (12.7)
End Stage Disease Leading to Transplantation - n (%)	Glomerulonephritis / glomerular disease	14 (21.5)	6 (15.8)	11 (15.5)
	Pyelonephritis	2 (3.1)	0	2 (2.8)
	Polycystic disease	8 (12.3)	6 (15.8)	14 (19.7)
	Hypertension / nephrosclerosis	9 (13.9)	5 (13.2)	8 (11.3)
	Drug induced toxicity	1 (1.5)	0	0
	Diabetes mellitus	7 (10.8)	3 (7.9)	4 (5.6)
	Interstitial nephritis	1 (1.5)	3 (7.9)	1 (1.4)
	Obstructive disorder / reflux	3 (4.6)	1 (2.6)	2 (2.8)
	Unknown	14 (21.5)	10 (26.3)	20 (28.2)
	Other	6 (9.2)	4 (10.5)	9 (12.7)
Pre-Op status - n (%)	None	11 (16.9)	8 (21.1)	13 (18.3)
	Hemodialysis	42 (64.6)	25 (65.8)	52 (73.2)
	Peritoneal dialysis	12 (18.5)	5 (13.2)	6 (8.5)
Panel Reactive Antibodies - Most Recent Evaluation (%)	n	65	38	71
	Mean	1.0	1.2	1.0
	SD	4.56	4.20	2.48
	Median	0	0	0
	Range	0, 27.0	0, 24.0	0, 12.0
Cold Ischemia Time (h)	n	32	19	25
	Mean	15.1	15.4	15.9
	SD	4.98	5.43	3.92
	Median	16.0	16.2	16.1
	Range	4.0, 22.9	5.0, 23.2	8.0, 23.7

Cold ischemia time is based on deceased donors only

Donor characteristics – Extension ITT analysis set

		Neoral + Certican N= 65	**AEB 200mg bid + Certican N= 38**	**AEB 300mg bid + Certican N= 71**
Donor Age (years)	n	65	38	71
	Mean	43.2	43.7	42.9
	SD	11.69	13.24	11.80
	Median	44.0	45.0	45.0
	Range	15, 65	13, 69	16, 65
Donor characteristic – n (%)	Living related	25 (38.5)	14 (36.8)	29 (40.8)
	Living unrelated	8 (12.3)	5 (13.2)	17 (23.9)
	Deceased heart beating	32 (49.2)	19 (50.0)	25 (35.2)

Outcome Measures

Primary outcome Result(s)

Renal function

Calculated GFR using MDRD formula, by visit window – Extension safety analysis set

Calculated GFR using MDRD formula, by visit window – Extension safety analysis set	Neoral + Certican				AEB 200mg bid + Certican				AEB 300mg bid + Certican				Group difference	
Visit Window	N	Mean	SD	Median	N	Mean	SD	Median	N	Mean	SD	Median	AEB 200mg bid - Neoral P-value	AEB 300mg bid - Neoral P-value
Week 1	65	47.9	22.95	48.0	36	56.5	26.14	58.0	69	55.9	26.16	54.0	0.040	0.061
Month 1	66	59.0	19.72	57.5	37	64.5	18.83	66.0	70	67.1	20.83	64.5	0.094	0.009
Month 3	64	56.5	17.07	52.0	36	63.9	14.56	66.0	68	67.8	19.85	65.0	0.004	<.001
Month 6	65	57.0	14.53	56.0	37	59.7	13.17	61.0	69	65.9	19.55	62.0	0.164	0.002
Month 12	66	57.8	15.06	57.0	36	59.5	16.74	61.0	70	65.2	18.09	60.5	0.649	0.030
Month 15	58	55.3	13.77	54.0	33	58.1	13.58	60.0	68	65.5	17.94	64.0	0.249	<.001
Month 18	60	55.6	13.14	54.0	32	59.4	14.91	59.5	66	64.1	17.76	61.5	0.243	0.006
Month 21	56	56.0	15.61	53.5	32	59.3	17.40	59.0	67	64.5	18.87	63.0	0.407	0.011
Month 24	58	56.1	15.77	56.0	30	58.8	14.61	60.0	65	63.0	17.79	59.0	0.289	0.042
Month 30	43	55.5	15.25	53.0	27	58.5	12.35	59.0	59	61.4	18.73	60.0	0.186	0.095
Month 36	27	50.4	14.73	49.0	10	63.0	12.40	65.0	45	61.4	20.14	59.0	0.023	0.020

Calculated GFR using MDRD formula, by visit window – Extension safety analysis set	Neoral + Certican				AEB 200mg bid + Certican				AEB 300mg bid + Certican				Group difference	
Visit Window	N	Mean	SD	Median	N	Mean	SD	Median	N	Mean	SD	Median	AEB 200mg bid - Neoral P-value	AEB 300mg bid - Neoral P-value
Month 42	20	51.3	16.50	51.0	0				31	59.5	19.81	60.0		0.127
Month 48	18	56.9	17.88	57.5	0				31	59.2	17.01	58.0		0.709
Month 54	8	53.5	18.38	52.0	0				14	59.5	22.91	56.0		0.561
Month 60	1	45.0		45.0	0				0					

Data collected more than 2 days after discontinuation of study medication are not included in this table.

P-value is based on Wilcoxon's rank sum test.

Secondary Outcome Result(s)

Composite efficacy failure

Analysis of the first efficacy failure event for the extension phase – Extension ITT analysis set

				Difference to control	
	Neoral + Certican N=65	AEB 200mg bid + Certican N=38	AEB 300mg bid + Certican N=71	AEB 200mg bid - Neoral	AEB 300mg bid - Neoral
Composite efficacy failure (Month 12)					
Number of events	1	4	1		
K-M failure rate (%)	1.5	10.5	1.4	9.0	-0.1
95% confidence interval (%)	(0.0, 4.5)	(0.8, 20.3)	(0.0, 4.1)	(-1.2,19.2)	(-4.2,3.9)
Treated BPAR (Month 12)					
Number of events	1	4	1		
K-M failure rate (%)	1.5	10.5	1.4	9.0	-0.1
95% confidence interval (%)	(0.0, 4.5)	(0.8, 20.3)	(0.0, 4.1)	(-1.2,19.2)	(-4.2,3.9)
Composite efficacy failure (Month 18)					
Number of events	2	7	1		
K-M failure rate (%)	3.1	18.4	1.4	15.3	-1.7
95% confidence interval (%)	(0.0, 7.3)	(6.1, 30.7)	(0.0, 4.1)	(2.3,28.4)	(-6.7,3.3)
Treated BPAR (Month 18)					
Number of events	2	6	1		
K-M failure rate (%)	3.1	15.8	1.4	12.7	-1.7
95% confidence interval (%)	(0.0, 7.3)	(4.2, 27.4)	(0.0, 4.1)	(0.4,25.0)	(-6.7,3.3)
Composite efficacy failure (Month 24)					
Number of events	4	7	3		
K-M failure rate (%)	6.2	18.4	4.2	12.3	-1.9
95% confidence interval (%)	(0.3, 12.0)	(6.1, 30.7)	(0.0, 8.9)	(-1.4,25.9)	(-9.4,5.6)
Treated BPAR (Month 24)					
Number of events	3	6	1		
K-M failure rate (%)	4.6	15.8	1.4	11.1	-3.2
95% confidence interval (%)	(0.0, 9.8)	(4.2, 27.4)	(0.0, 4.1)	(-1.5,23.8)	(-9.0,2.6)

Composite efficacy failure (Month 30)					
Number of events	6	7	4		
K-M failure rate (%)	9.4	18.4	5.7	9.0	-3.7
95% confidence interval (%)	(2.2, 16.6)	(6.1, 30.7)	(0.3, 11.2)	(-5.3,23.2)	(-12.7,5.3)
Treated BPAR (Month 30)					
Number of events	3	6	1		
K-M failure rate (%)	4.6	15.8	1.4	11.1	-3.2
95% confidence interval (%)	(0.0, 9.8)	(4.2, 27.4)	(0.0, 4.1)	(-1.5,23.8)	(-9.0,2.6)
Composite efficacy failure (Month 36)					
Number of events	6		6		
K-M failure rate (%)	9.4		9.2		-0.2
95% confidence interval (%)	(2.2, 16.6)		(2.1, 16.3)		(-10.3,9.9)
Treated BPAR (Month 36)					
Number of events	3		1		
K-M failure rate (%)	4.6		1.4		-3.2
95% confidence interval (%)	(0.0, 9.8)		(0.0, 4.1)		(-9.0,2.6)
Composite efficacy failure (Month 42)					
Number of events	6		7		
K-M failure rate (%)	9.4		11.3		1.9
95% confidence interval (%)	(2.2, 16.6)		(3.3, 19.4)		(-8.9,12.7)
Treated BPAR (Month 42)					
Number of events	3		1		
K-M failure rate (%)	4.6		1.4		-3.2
95% confidence interval (%)	(0.0, 9.8)		(0.0, 4.1)		(-9.0,2.6)
Composite efficacy failure (Month 48)					
Number of events	9		10		
K-M failure rate (%)	20.8		17.7		-3.1
95% confidence interval (%)	(7.2, 34.3)		(7.5, 27.9)		(-20.0,13.8)
Treated BPAR (Month 48)					
Number of events	4		2		
K-M failure rate (%)	8.6		3.9		-4.7
95% confidence interval (%)	(0.0, 17.7)		(0.0, 9.3)		(-15.3,5.9)
Composite efficacy failure (Month 54)					
Number of events	9		11		
K-M failure rate (%)	20.8		20.3		-0.5

95% confidence interval (%)	(7.2, 34.3)	(9.2, 31.3)	(-18.0,17.0)
Treated BPAR (Month 54)			
Number of events	4	2	
K-M failure rate (%)	8.6	3.9	-4.7
95% confidence interval (%)	(0.0, 17.7)	(0.0, 9.3)	(-15.3,5.9)

1. Composite efficacy failure: Treated BPAR, graft loss, death, or lost to follow-up.
2. K-M = Kaplan-Meier, negative differences favor AEB071.
3. tBPAR: Treated biopsy proven acute rejection

Safety Results

Incidence of AEs by primary system organ class – Extension safety analysis set

Primary system organ class	Neoral +Certican N=66	AEB 200mg bid +Certican N=38	AEB 300mg bid +Certican N=70
Patients with at least one AE	65 (98.5)	38 (100.0)	70 (100.0)
Infections and infestations	55 (83.3)	36 (94.7)	66 (94.3)
Gastrointestinal disorders	47 (71.2)	34 (89.5)	64 (91.4)
Metabolism and nutrition disorders	55 (83.3)	33 (86.8)	61 (87.1)
Skin and subcutaneous tissue disorders	39 (59.1)	30 (78.9)	53 (75.7)
General disorders and administration site conditions	42 (63.6)	29 (76.3)	51 (72.9)
Vascular disorders	39 (59.1)	27 (71.1)	40 (57.1)
Injury, poisoning and procedural complications	38 (57.6)	24 (63.2)	45 (64.3)
Investigations	30 (45.5)	22 (57.9)	28 (40.0)
Renal and urinary disorders	39 (59.1)	20 (52.6)	41 (58.6)
Musculoskeletal and connective tissue disorders	33 (50.0)	18 (47.4)	46 (65.7)
Respiratory, thoracic and mediastinal disorders	24 (36.4)	16 (42.1)	29 (41.4)
Blood and lymphatic system disorders	34 (51.5)	13 (34.2)	35 (50.0)
Nervous system disorders	38 (57.6)	13 (34.2)	26 (37.1)
Cardiac disorders	17 (25.8)	12 (31.6)	20 (28.6)
Reproductive system and breast disorders	17 (25.8)	8 (21.1)	20 (28.6)
Eye disorders	13 (19.7)	7 (18.4)	13 (18.6)
Psychiatric disorders	18 (27.3)	6 (15.8)	9 (12.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (28.8)	5 (13.2)	12 (17.1)
Immune system disorders	7 (10.6)	4 (10.5)	4 (5.7)
Ear and labyrinth disorders	3 (4.5)	2 (5.3)	6 (8.6)
Endocrine disorders	7 (10.6)	2 (5.3)	8 (11.4)
Hepatobiliary disorders	5 (7.6)	2 (5.3)	10 (14.3)
Surgical and medical procedures	1 (1.5)	1 (2.6)	2 (2.9)

Congenital, familial and genetic disorders	2 (3.0)	0	4 (5.7)
Adverse events for the entire period, related to study drug,	58 (87.9)	30 (78.9)	65 (92.9)

AEs by SOC are presented in descending order of frequency in AEB071 200 mg group

Number (%) of patients reporting AEs (≥10% in any group) for the entire period by system organ class and preferred term – Extension safety analysis set

	Neoral + Certican N=66	AEB 200mg bid + Certican N=38	AEB 300mg bid + Certican N=70
Total number of patients with AEs	65 (98.5)	38 (100.0)	70 (100.0)
Blood and lymphatic system disorders			
Anemia	21 (31.8)	8 (21.1)	29 (41.4)
Cardiac disorders			
Tachycardia	6 (9.1)	7 (18.4)	10 (14.3)
Gastrointestinal disorders			
Constipation	26 (39.4)	21 (55.3)	41 (58.6)
Diarrhea	17 (25.8)	12 (31.6)	44 (62.9)
Vomiting	13 (19.7)	11 (28.9)	31 (44.3)
Nausea	23 (34.8)	9 (23.7)	31 (44.3)
Abdominal pain upper	8 (12.1)	8 (21.1)	15 (21.4)
Abdominal pain	7 (10.6)	7 (18.4)	13 (18.6)
Aphthous stomatitis	7 (10.6)	6 (15.8)	7 (10.0)
Dyspepsia	3 (4.5)	6 (15.8)	10 (14.3)
Gastroesophageal reflux disease	0	1 (2.6)	8 (11.4)
General disorders and administration site conditions			
Edema peripheral	33 (50.0)	20 (52.6)	35 (50.0)
Pyrexia	16 (24.2)	14 (36.8)	13 (18.6)
Asthenia	0	5 (13.2)	3 (4.3)
Fatigue	3 (4.5)	4 (10.5)	7 (10.0)
Non-cardiac chest pain	5 (7.6)	1 (2.6)	7 (10.0)
Immune system disorders			
Kidney transplant rejection	6 (9.1)	4 (10.5)	0
Infections and infestations			
Urinary tract infection	22 (33.3)	14 (36.8)	36 (51.4)
Gastroenteritis	9 (13.6)	8 (21.1)	12 (17.1)
Upper respiratory tract infection	18 (27.3)	8 (21.1)	19 (27.1)
Nasopharyngitis	9 (13.6)	5 (13.2)	6 (8.6)
Tinea pedis	3 (4.5)	5 (13.2)	9 (12.9)
Pneumonia	4 (6.1)	1 (2.6)	9 (12.9)
Injury, poisoning and procedural complications			

Procedural pain	10 (15.2)	4 (10.5)	6 (8.6)
Complications of transplanted kidney	11 (16.7)	3 (7.9)	12 (17.1)
Incision site pain	9 (13.6)	2 (5.3)	8 (11.4)
Incisional hernia	5 (7.6)	1 (2.6)	7 (10.0)
Wound dehiscence	5 (7.6)	1 (2.6)	7 (10.0)
Investigations			
Blood creatinine increased	12 (18.2)	7 (18.4)	8 (11.4)
Weight increased	4 (6.1)	6 (15.8)	6 (8.6)
Hepatic enzyme increased	0	4 (10.5)	3 (4.3)
Metabolism and nutrition disorders			
Dyslipidemia	16 (24.2)	13 (34.2)	14 (20.0)
Hypocalcaemia	9 (13.6)	10 (26.3)	11 (15.7)
Hypophosphatemia	12 (18.2)	8 (21.1)	12 (17.1)
Hypercholesterolemia	17 (25.8)	7 (18.4)	11 (15.7)
Hyperglycemia	8 (12.1)	7 (18.4)	11 (15.7)
Hypomagnesaemia	18 (27.3)	5 (13.2)	4 (5.7)
Hypertriglyceridemia	9 (13.6)	4 (10.5)	13 (18.6)
Diabetes mellitus	7 (10.6)	3 (7.9)	7 (10.0)
Hyperkalemia	12 (18.2)	3 (7.9)	5 (7.1)
Hypokalemia	12 (18.2)	3 (7.9)	26 (37.1)
Hyperlipidemia	8 (12.1)	2 (5.3)	8 (11.4)
Musculoskeletal and connective tissue disorders			
Pain in extremity	15 (22.7)	9 (23.7)	12 (17.1)
Arthralgia	7 (10.6)	4 (10.5)	14 (20.0)
Back pain	10 (15.2)	4 (10.5)	6 (8.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic nevus	8 (12.1)	1 (2.6)	4 (5.7)
Skin papilloma	7 (10.6)	0	2 (2.9)
Nervous system disorders			
Headache	20 (30.3)	7 (18.4)	13 (18.6)
Dysgeusia	1 (1.5)	2 (5.3)	9 (12.9)
Tremor	10 (15.2)	2 (5.3)	0
Psychiatric disorders			
Insomnia	15 (22.7)	2 (5.3)	3 (4.3)
Renal and urinary disorders			
Hematuria	5 (7.6)	7 (18.4)	11 (15.7)
Proteinuria	17 (25.8)	7 (18.4)	17 (24.3)
Dysuria	9 (13.6)	6 (15.8)	11 (15.7)
Renal impairment	6 (9.1)	5 (13.2)	1 (1.4)
Reproductive system and breast disorders			

Erectile dysfunction	5 (7.6)	2 (5.3)	8 (11.4)
Respiratory, thoracic and mediastinal disorders			
Cough	9 (13.6)	7 (18.4)	15 (21.4)
Epistaxis	5 (7.6)	5 (13.2)	1 (1.4)
Skin and subcutaneous tissue disorders			
Acne	15 (22.7)	11 (28.9)	16 (22.9)
Pruritus	2 (3.0)	5 (13.2)	9 (12.9)
Erythema	4 (6.1)	4 (10.5)	5 (7.1)
Hypertrichosis	14 (21.2)	2 (5.3)	7 (10.0)
Vascular disorders			
Hypertension	24 (36.4)	15 (39.5)	22 (31.4)
Lymphocele	12 (18.2)	6 (15.8)	10 (14.3)
Hypotension	3 (4.5)	2 (5.3)	10 (14.3)

System organ classes are presented alphabetically; preferred terms are presented in descending order of frequency in AEB071 200 mg group within system organ classes

Number (%) of patients reporting infections for the entire period by type of organism – Extension safety analysis set

	Neoral + Certican N=66	AEB 200mg bid + Certican N=38	AEB 300mg bid + Certican N=70
Total number of patients with infections	56 (84.8)	37 (97.4)	67 (95.7)
Total number of patients with serious infections	26 (39.4)	14 (36.8)	32 (45.7)
Type of Organism			
Bacterial	29 (43.9)	16 (42.1)	42 (60.0)
Fungal	4 (6.1)	7 (18.4)	12 (17.1)
Other	29 (43.9)	17 (44.7)	40 (57.1)
Unknown	29 (43.9)	17 (44.7)	30 (42.9)
Viral	21 (31.8)	11 (28.9)	19 (27.1)

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them for the entire period – Extension safety analysis set

	Neoral + Certican N=66 n (%)	AEB 200mg bid + Certican N=38 n (%)	AEB 300mg bid + Certican N=70 n (%)
Death	1 (1.5)	0	3 (4.3)
SAE(s)	44 (66.7)	26 (68.4)	48 (68.6)
Clinically significant AE(s)/infection(s)	36 (54.5)	19 (50.0)	41 (58.6)
Discontinued study medication due to AE(s)	11 (16.7)	7 (18.4)	12 (17.1)

Dose reduction/interruption due to AE(s)	29 (43.9)	15 (39.5)	39 (55.7)

1) Clinically significant AEs are the AEs which lead to continuation/reduction/interruption of study medication.

2) 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

20 Feb 2013

Date Inclusion Novartis Clinical trial Results Database

11 Apr 2013

Date of Latest Update

12 Mar 2013