Sponsor

Novartis AG

Generic Drug Name

Sotrastaurin

Trial Indication(s)

Renal transplantation

Protocol Number

CAEB071A2203/CAEB071A2203E1

EudraCT no. 2005-003494-25 / 2007-002986-11

Protocol Title

12-month open label, randomized, multicenter study evaluating efficacy, safety and tolerability of oral AEB071 plus tacrolimus (converted to myfortic® after 3 months) vs. myfortic® plus tacrolimus in de novo renal transplant recipients

Clinical Trial Phase

Phase IIA

Study Start/End Dates

06-Oct-2006 to 20-May-2008

Reason for Termination (If applicable)

The study was prematurely terminated at the recommendation of the Data Monitoring Committee.

Study Design/Methodology

This was a 12-month, randomized, multi-center, open label, parallel group 3-arm study (two AEB071 treatment arms and a control arm (tacrolimus standard exposure)). In the AEB071 treatment arms the patients received tacrolimus as immunosuppressive regimen. After the Month 3 visit the patients had started on an AEB071 + tacrolimus regimen and were converted to a CNI-free regimen of AEB071 + myfortic after month 3. In all arms, patients received Simulect® as induction therapy and corticosteroids.

Centers

28 centers in 8 countries: Canada (6), France (12), Germany (92), Italy (18), Spain (22), Switzerland (32), United Kingdom (20) and United States *(*14)

Objectives:

Primary objective(s)

The primary objective of the study was to demonstrate that in *de novo* renal transplant patients, at least one of the AEB071 treatment regimens is not inferior to the myfortic (MPA) treatment regimen (myfortic + tacrolimus) within 6 months of the initial dose of study drug with respect to primary efficacy failure, defined as a composite efficacy endpoint of treated BPAR, graft loss, death or loss to follow-up.

Secondary objective(s)

To evaluate the AEB071 regimens in comparison to the control arm with respect to primary efficacy failure at Month 3 post-transplant.

To compare the safety and tolerability in the AEB071 treatment arms and the control arm.

The main safety objective was to compare renal function in the AEB071 treatment arms to the control arm at Month 6 post-transplant (MDRD formula for GFR).

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

The investigational drug was AEB071. The drug was provided by Novartis as 100 mg hard gelatin capsules for oral administration and supplied in bottles.

Statistical Methods

The primary efficacy analysis used the Kaplan-Meier (KM) methodology to estimate event rates for the ITT population. Greenwood's formula was used to estimate standard errors and to derive the twosided 95% confidence interval from the Z-test statistic distribution for the difference in event rates between the AEB071 and control arms.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Participation in core study CAEB071A2203
- The patient has been maintained on AEB071/mycophenolic acid or tacrolimus/mycophenolic acid, consistent with their original randomization, at their core study Month 12 visit.
- Women capable of becoming pregnant are required to practice a medically approved method of birth control as long as they are on study medication and for a period of 3 months following discontinuation of study drug(s).

Exclusion criteria:

- Pregnancy. Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Patient disposition, by treatment (randomised population)

	Myfortic 720mg & TAC SE	AEB071 200mg & TAC SE	AEB071 200mg & TAC RE
Number (%) of patients			
Randomized (ITT analysis set)	74 (100)	76 (100)	66 (100)
Safety population 1	74 (100)	75 (98.7)	65 (98.5)
Safety population 2	55 (74.3)	53 (69.7)	42 (63.6)
Study medication completion			
Completed study medication	12 (16.2)	6 (7.9)	15 (22.7)
Discontinued study medication	62 (83.8)	70 (92.1)	51 (77.3)
Study completion			
Completed study	22 (29.7)	26 (34.2)	30 (40.5)
Discontinued study (withdrawal)	52 (70.3)	50 (65.8)	36 (54.5)
Main reason for discontinuation of study medication			
Adverse event(s)	12 (16.2)	14 (18.4)	8 (12.1)
Abnormal laboratory value(s)	3 (4.1)	4 (5.3)	6 (9.1)
Abnormal test procedure result(s)	1 (1.4)	2 (2.6)	2 (3.0)
Unsatisfactory therapeutic effect	4 (5.4)	22 (28.9)	13 (19.7)
Protocol violation(s)	4 (5.4)	3 (3.9)	4 (6.1)
Subject withdrew consent	0	2 (2.6)	1 (1.5)
Administrative problems	38 (51.4)	23 (30.3)	16 (24.2)
Death	0	0	1 (1.5)
Main reasons for discontinuation of the study			
Subject withdrew consent	0	6 (7.9)	0
Lost to follow-up	1 (1.4)	1 (1.3)	0
Administrative problems	49 (66.2)	42 (55.3)	34 (51.5)
Death	2 (2.7)	1 (1.3)	2 (3.0)

The percentages are based on the number of randomised patients.

Baseline Characteristics

Recipient demographic summary and disease characteristics by treatment group (ITT analysis set)

		Myfortic 720mg & TAC SE	AEB071 200mg & TAC SE	AEB071 200mg & TAC RE
Age (years)	n	74	76	66
	Mean	44.6	43.7	44.9
	Median	45.0	44.0	43.5
	SD	11.62	11.01	11.87
	Range	19-70	18-65	18-67

Age group - n (%)	<65	72 (97.3)	75 (98.7)	64 (97.0)
	>65	2 (2.7)	1 (1.3)	2 (3.0)
Gender - n (%)	Male	53 (71.6)	54 (71.1)	48 (72.7)
	Female	21 (28.4)	22 (28.9)	18 (27.3)
Race - n (%)	Caucasian	71 (95.9)	73 (96.1)	63 (95.5)
	Black	2 (2.7)	1 (1.3)	1 (1.5)
	Asian	1 (1.4)	0	0
	Other	0	1 (1.3)	2 (3.0)
	Pacific Islander	0	1 (1.3)	0
Weight (kg)	N	69	72	61
	Mean	79.6	78.1	76.7
	SD	15.91	16.70	15.10
	Median	77.9	79.0	75.2
	Range	52-127	48-110	47-121
End stage disease leading to transplantation – n (%)				
Glomerulonephritis		21 (28.4)	16 (21.1)	14 (21.2)
Pyelonephritis		3 (4.1)	3 (3.9)	4 (6.1)
Polycystic disease		15 (20.3)	15 (19.7)	13 (19.7)
Hypertension/nephrosclerosis		5 (6.8)	9 (11.8)	2 (3)
Drug induced toxicity		0	1 (1.3)	0
Diabetes mellitus		5 (6.8)	2 (2.6)	1 (1.5)
Interstitial nephritis		0	0	3 (4.5)
Vasculitis		1 (1.4)	1 (1.3)	0
Obstructive disorder/reflux		3 (4.1)	2 (2.6)	4 (6.1)
Renal hyperplasia/dysplasia		0	1 (1.3)	0
Unknown		5 (6.8)	5 (6.6)	4 (6.1)
Other		16 (21.6)	21 (27.6)	20 (30.3)
Current dialysis – n (%)				
None		11 (14.9)	9 (11.8)	10 (15.2)
Hemodialysis		46 (62.2)	58 (76.3)	46 (69.7)
Peritoneal dialysis		17 (23)	9 (11.8)	9 (13.6)

Summary of Efficacy

Primary Outcome Result(s)

Comparison of Kaplan-Meier estimates of first efficacy events (local pathology, ITT population, *de novo* period and final analysis)

	Myfortic 720mg & TAC SE	AEB071 200mg & TAC SE	AEB071 200mg & TAC RE
	***De novo* period**		
Composite efficacy failure			
Number of events	3	4	1
K-M failure rate (%)	4.1	5.4	1.5
Difference from control (%), 95% CI (%)	NA	1.2 (-5.6, 8.1)	-2.6 (-8.1, 2.9)
Treated BPAR ≥1A			
Number of events	2	3	1
K-M failure rate (%)	2.8	4.1	1.5%
Difference from control (%), 95% CI (%)	NA	1.3 (-4.6, 7.2)	-1.2 (-6.0, 3.6)
	Final analysis		
Composite efficacy failure			
Number of events	5	24	14
K-M failure rate (%)	7.8	44.8	34.1
Difference from control (%), 95% CI (%)	NA	37.0 (21.5, 52.5)	26.2 (9.0, 43.5)
BPAR ≥1A			
Number of events	3	21	13
K-M failure rate (%)	4.6	40.2	32.4
Difference from control (%), 95% CI (%)	NA	35.6 (20.9, 50.3)	27.7 (11.0, 44.5)

Composite primary efficacy failure: treated BPAR, graft loss, death or lost to follow-up.
Events occurring up to 7 days after last dose of study medication are included in the analysis.
De novo period comparison is of KM estimates on Day 104

Final analysis: comparison is of KM estimates at Day 286

CI = Confidence interval; KM = Kaplan-Meier, negative differences favor AEB071.

Secondary Outcome Result(s)

Comparison of Kaplan-Meier estimates of first efficacy events (local pathology) ITT population: Final analysis

Endpoint	Myfortic 720mg + TAC SE (a) (N=74) Number w/event	KM est.	AEB071 200mg + TAC SE (b) (N=76) Number w/event	KM est.	AEB071 200mg + TAC RE (c) (N=66) Number w/event	KM est.	95% CI for difference (b)-(a)	95% CI for difference (c)-(a)
Comp. Efficacy Failure: Treated BPAR>=1A, graft loss, death, or lost to follow-up	5	7.8	24	44.8	14	34.1	37.0 (21.5,52.5)	26.2 (9.0,43.5)
Comp. Efficacy Failure: Treated BPAR >=1A, graft loss, death, or lost to follow-up + conversion failures	9	13.7	28	48.4	20	41.4	34.7 (18.8,50.6)	27.7 (10.3,45.0)
Treated biopsy proven rejection >= 1A	3	4.6	21	40.2	13	32.4	35.6 (20.9,50.3)	27.7 (11.0,44.5)
Treated biopsy proven acute rejection, graft loss or death	5	7.8	21	40.2	14	34.1	32.4 (17.1,47.7)	26.2 (9.0,43.5)
Death or graft Loss	2	3.2		0.0	1	2.4	-3.2 (-7.7,1.2)	-0.8 (-7.3,5.6)
Graft loss	1	1.4		0.0		0.0	-1.4 (-4.0,1.3)	-1.4 (-4.0,1.3)
Death	1	1.9		0.0	1	2.4	-1.9 (-5.5,1.8)	0.5 (-5.4,6.4)

Loss to follow-up	1	1.4	3	7.4		0.0	6.0 (-3.6,15.7)	-1.4 (-4.0,1.3)
Treated acute rejection	4	6.2	22	41.2	13	32.4	35.0 (20.0,49.9)	26.1 (9.1,43.2)
Treated acute rejection Graft loss, death, or loss to follow-up	6	9.4	25	45.7	14	34.1	36.4 (20.7,52.0)	24.7 (7.3,42.1)
Converted to standard of care after failing conversion eligibility criteria	5	7.8	4	6.4	7	12.6	-1.4 (-10.3,7.5)	4.8 (-6.1,15.7)

Note: 1. TAC SE = Tacrolimus standard exposure, TAC RE = Tacrolimus reduced exposure. In the AEB071 arms, tacrolimus is switched to Myfortic 720 mg after Month 3. Myfortic and AEB071 are given bid.
2. Kaplan-Meier estimates are given at Day=286.

Comparison of Kaplan-Meier estimates of first efficacy events (local pathology) ITT population: De-novo period

Endpoint	Myfortic 720mg + TAC SE (a) (N=74) Number w/event	KM est.	AEB071 200mg + TAC SE (b) (N=76) Number w/event	KM est.	AEB071 200mg + TAC RE (c) (N=66) Number w/event	KM est.	95% CI for difference (b)-(a)	(c)-(a)
Comp. Efficacy Failure: Treated BPAR>=1A, graft loss, death, or lost to follow-up	3	4.1	4	5.4	1	1.5	1.2 (-5.6,8.1)	-2.6 (-8.1,2.9)
Comp. Efficacy Failure: Treated BPAR >=1A, graft loss, death, or lost to follow-up + conversion failures	7	10.3	7	10.0	5	8.5	-0.3 (-10.4,9.8)	-1.7 (-11.9,8.5)
Treated biopsy proven rejection >= 1A	2	2.8	3	4.1	1	1.5	1.3 (-4.6,7.2)	-1.2 (-6.0,3.6)
Treated biopsy proven acute rejection, graft loss or death	3	4.1	3	4.1	1	1.5	-0.1 (-6.5,6.3)	-2.6 (-8.1,2.9)
Death or graft Loss	1	1.4		0.0		0.0	-1.4 (-4.0,1.3)	-1.4 (-4.0,1.3)
Graft loss	1	1.4		0.0		0.0	-1.4 (-4.0,1.3)	-1.4 (-4.0,1.3)
Death		0.0		0.0		0.0	0.0 (0.0,0.0)	0.0 (0.0,0.0)

Loss to follow-up	1	1.4	1	1.3		0.0	-0.0 (-3.8,3.7)	-1.4 (-4.0,1.3)
Treated acute rejection	3	4.4	4	5.6	1	1.5	1.2 (-6.0,8.5)	-2.8 (-8.6,2.9)
Treated acute rejection Graft loss, death, or loss to follow-up	4	5.7	5	6.9	1	1.5	1.2 (-6.8,9.2)	-4.2 (-10.4,2.0)
Converted to standard of care after failing conversion eligibility criteria	5	7.8	3	4.8	4	7.1	-2.9 (-11.4,5.5)	-0.6 (-10.0,8.7)

Note: 1. TAC SE = Tacrolimus standard exposure, TAC RE = Tacrolimus reduced exposure. In the AEB071 arms, tacrolimus is switched to Myfortic 720 mg after Month 3. Myfortic and AEB071 are given bid.
2. Kaplan-Meier estimates are given at Day=104.

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Number (%) of patients who died, had graft loss, or discontinuations of study medication due to AEs/infections (safety population 1, final analysis)

	Myfortic 720mg & TAC SE	AEB071 200mg & TAC SE	AEB071 200mg & TAC RE
n	74	75	65
Death	1 (1.4)	1 (1.3)	1 (1.5)
Graft loss	1 (1.4)	1 (1.3)	0
SAEs	32 (43.2)	37 (49.3)	41 (63.1)
Clinical significant AE(s)	47 (63.5)	39 (52.0)	32 (49.2)
Discontinued study medication due to AE(s)/infection(s)	12 (16.2)	24 (32.0)	18 (27.7)
Dose reduction/interruption due to AE(s)/infection(s)	42 (56.8)	27 (36.0)	24 (36.9)

SAEs (including graft loss) and deaths are included up to 30 days after last study medication and clinically significant AEs up to 7 days after last study medication are included.

Other Adverse Events by System Organ Class

Number (%) of patients reporting AEs (≥ 10% in any group) by system organ class, preferred term, and treatment (safety population 1, final analysis)

Adverse event (MedDRA preferred term)	Myfortic 720mg & TAC SE n (%)	AEB071 200mg & TAC SE n (%)	AEB071 200mg & TAC RE n (%)
n	74	75	65
Patients with AEs	74 (100)	71 (94.7)	65 (100)
Patients with SAEs	32 (43.2)	37 (49.3)	41 (63.1)
Blood and lymphatic disorders			
Anaemia	16 (21.6)	19 (25.3)	12 (18.5)
Leukocytosis	5 (6.8)	14 (18.7)	6 (9.2)
Leucopenia	10 (13.5)	2 (2.7)	4 (6.2)
Cardiac disorders			
Tachycardia	1 (1.4)	12 (16.0)	12 (18.5)
Gastrointestinal disorders			
Abdominal pain	12 (16.2)	6 (8.0)	5 (7.7)
Abdominal pain, upper	10 (13.5)	9 (12.0)	4 (6.2)
Constipation	19(25.7)	28 (37.3)	21 (32.3)
Diarrhea	38 (51.4)	31 (41.3)	25 (38.5)
Dyspepsia	10 (13.5)	6 (8.0)	5 (7.7)
Flatulence	10 (13.5)	4 (5.3)	8 (12.3)
Nausea	19 (25.7)	26 (34.7)	18 (27.7)
Vomiting	12(16.2)	15 (20.0)	18 (27.7)
General disorders and administration site conditions			
Oedema	10 (13.5)	14 (18.7)	10 (15.4)
Oedema peripheral	14 (18.9)	10 (13.3)	14 (21.5)
Pain	2 (2.7)	8 (10.7)	1 (1.5)
Pyrexia	7 (9.5)	8 (10.7)	11 (16.9)
Infections and infestations			
Cytomegalovirus	3 (4.1)	4 (5.3)	7 (10.8)
Nasopharyngitis	10 (13.5)	9 (12.0)	12 (18.5)
Urinary tract infection	25 (33.8)	28 (37.3)	21 (32.3)
Injury, poisoning and procedural complications			
Procedural pain	17 (23.0)	14 (18.7)	12 (18.5)
Wound complication	10 (13.5)	11 (14.7)	6 (9.2)
Investigations			
Blood creatinine increased	9 (12.2)	22 (29.3)	18 (27.7)
Metabolism and nutrition disorders			
Diabetes mellitus	11 (14.9)	5 (6.7)	5 (7.7)

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report

27-May-2009

Date of Inclusion in The Novartis Trial Results Database

28-May-2009 core
13-Feb 2016 updated with extension study data