Sponsor

Novartis AG

Generic Drug Name

Sotrastaurin acetate

Therapeutic Area of Trial

Renal transplantation

Approved Indication

Investigational

Study Number

CAEB071A2207

Title

A 12-month open-label, randomized, multi-center, sequential cohort, dose finding study to evaluate the efficacy, safety and tolerability of oral AEB071 versus tacrolimus in combination with *myfortic*®, Simulect® and corticosteroids in *de novo* adult renal transplant recipients

Phase of Development

Phase IIa and IIb

Study Start/End Dates

12 Jun 2007 to 20 May 2008

Study Design/Methodology

A 12-month, randomized, multi-center, open label study in 2 stages (Stage 1, Phase IIa, efficacy and Stage 2, Phase IIb, dose-finding). Stage 1 began with 2 arms (one AEB071 arm with 300mg b.i.d. and a control arm). Once the initial 129 patients of Stage 1 had been randomized, (2:1 randomization), the trial would stop enrolling. 26 centers enrolled 125 out of 129 patients planned in Stage 1.When all patients reached 3 months post-transplantation, an interim analysis was planned. Based on the data from the interim analysis, enrollment into Stage 2 would have begun. However, the study was terminated prior to the 3-Month interim analysis in Stage 1 at the recommendation of the Data Monitoring Committee.

Centers

This was a global study with 26 enrolling centers. The following countries (number of centers) participated: USA (11), Germany (5), Sweden (2), Belgium (2), UK (2), Canada (2), Korea (1), and Spain (1).

Publication

None

Objectives

Primary objective(s)

- Compare, in Stage 1, the efficacy of AEB071 to that of tacrolimus, both in combination with myfortic (MPA), Simulect, and steroids, at Month 3.
- Main safety - Compare renal function in the AEB071 treatment arm with the control arm at Months 3 and Month 12.

Secondary objective(s)

- Determine the target range for AEB071 trough levels based on the relationship of trough levels with rejections (under-immunosuppression), and with BK-polyoma viremia and other infections (over-immunosuppression.).
- Determine the dose or concentration of AEB071 with the best benefit/risk profile.

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

AEB071 (Sotrastaurin acetate)100mg hard gelatin capsules for oral administration, were administered at initial dose of 300 mg bid.

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

- Tacrolimus (Prograf®) was dosed orally according to trough levels 8-15ng/mL at Month 1, 6-12ng/mL from Months 2-3, and 5-10ng/mL from Months 4-12.
- Myfortic® (mycophenolate acid sodium, MPA) was dosed in each arm at 720mg p.o. twice a day. All patients received Simulect® one vial i.v. within 12 hours prior to transplantation and again on Day 4.
- Corticosteroids were started orally 500mg at transplantation, 250mg the next day, 125mg on the 3rd day, 0.5mg/kg from Day 4 and then tapered to reach 5 to 10mg/day by the end of Month

Criteria for Evaluation

Primary variables

- The occurrence of a composite efficacy failure endpoint (treated biopsy-proven acute rejection (BPAR), graft loss, death or lost to follow-up) at Month 3 (cutoff was Day 104).

Safety and tolerability

- The calculated glomerular filtration rate (GFR) at Month 3 using the MDRD formula.
- The occurrence of adverse events (AE), serious AEs, infection, malignancy, as well as hematology, biochemistry laboratory, ECG results and vital signs.

Pharmacology

- Blood samples were collected at each visit for determination of trough levels of AEB071, MPA and tacrolimus. Only alert levels for AEB071 and myfortic were reported, however tacrolimus levels were reported for therapeutic drug monitoring purposes.

Abbreviated PK profiles of AEB071, the main metabolite AEE800, tacrolimus, and MPA levels were performed at selected trial sites with the required expertise and technical facilities in consenting patients.

Statistical Methods

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

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Male and female patients of any race ≥ 18 years old.
- Recipients of a primary kidney transplant from a deceased, living unrelated or non-HLA identical living related donor.
- Recipients of a kidney with a cold ischemic time (CIT) < 24 hours.
- Recipients of a kidney from a donor 10-65 years old.
- Patients expected to be able to take oral medication within 24 hours after graft reperfusion.

- Patients willing and capable of giving written informed consent for study participation an able to participate in the study for 12 months.

Exclusion Criteria

- Multi-organ transplant recipients or if the patient previously received an organ transplant.
- Recipients of an organ from a non-heart beating donor.
- Patients who were recipients of A-B-O incompatible transplants, all CDC cross match positive transplants.
- Patients without functional graft 24 hours after graft reperfusion; functional graft being defined as urine output of more than 250 mL/12 hours for patients without residual urinary output from native kidneys, or as a decrease in serum creatinine by **at least** 20% from pre-transplant.
- Patients with an absolute neutrophil count of < 1,500/mm3, or absolute leukocytes count < 2,500/mm3 or platelet count < 100,000/mm3 at screening.
- Patients who were treated with drugs that are strong inducers or inhibitors of cytochrome P450 3A4 at screening and could not discontinue this treatment.
- Patients with long QT-syndrome or QTc at baseline exceeding 500 msec, or who were treated with drugs inducing QT prolongation at screening, and could not have discontinued this treatment.
- Patients requiring antiarrhythmic drugs with QT-prolonging properties (such as amiodarone, sotalol, dofetilide, quinidine, procainamide, disopyramide).
- Patients with a family history of long QT syndrome or of sudden unexplained death.
- Patients with left branch bundle block (LBBB) or who experienced, during the previous 6 months, hospitalization for heart failure of cardiac etiology, or left-ventricular dysfunction (LVEF <40%)
- Patients with a history, in the preceding 3 months, of significant and persistent arrhythmias such as ventricular fibrillation or tachycardia, atrial fibrillation or flutter.
- Patients with symptomatic coronary artery disease.
- Use of other investigational drugs or a non-protocol immunosuppressant, including induction agents other than Simulect, at randomization, or within 30 days or 5 half-lives prior to randomization, whichever was longer
- History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures
- Patients who were anti-HIV-positive, or HBsAg-positive. Anti-HCV positive patients were excluded, except patients with negative PCR-result. Laboratory results obtained more than 6 months prior to study entry were to be repeated within the first week after randomization. Patients who were tested positive for any of the viral indicators after randomization were discontinued from study treatment.
- Recipients of a kidney from a donor who tested positive for HIV, HBsAg or anti-HCV
- Sensitized patients (most recent anti-HLA Class I Panel Reactive Antibodies > 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
- History of malignancy of any organ system, treated or untreated, within the past 5 years regard-

less of evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin (excised ≥ 2 years prior to randomization)

- Patients with severe systemic infections, current or within the 2 weeks prior to randomization.
- Patients with any history of significant coagulopathy or medical condition requiring long-term systemic anticoagulation after transplantation, which would interfere with obtaining biopsies. Low-dose Aspirin treatment (up to 200mg/day) was allowed. Plavix® was not allowed.
- Evidence of severe liver disease, including abnormal liver profile (aspartate aminotransferase [AST], alanine aminotransferase [ALT] or total bilirubin > 3 times upper limit of normal [ULN]) at screening.
- Patients with a severe digestive system disorder (including functional disorders) at screening.
- Patients with any condition which was expected to prohibit full-dose myfortic therapy or tacrolimus therapy
- Patients with any surgical or medical condition, which in the opinion of the investigator, precluded enrollment in this trial
- Patients who were unlikely to comply with the study requirements or unable to cooperate or communicate with the investigator
- Pregnant or nursing (lactating) women, and women who might become pregnant during the study

Number of Subjects

Patient disposition, by treatment (all randomized patients)

	Tac + MPA n (%)	AEB071 + MPA n (%)
Number (%) of patients		
Randomized (ITT analysis set)	44 (100.0)	81 (100.0)
Safety analysis set	44 (100.0)	81 (100.0)
Study medication completion		
Completed study medication	0	0
Discontinued study medication	44 (100.0)	81 (100.0)
Main reason for discontinuation of study medication		
Abnormal laboratory values(s)	0	0
Abnormal test procedure result(s)	0	0
Administrative problems	40 (90.9)	55 (67.9)
Adverse event(s)	1 (2.3)	10 (12.3)
Death	0	1 (1.2)
Graft loss	0	0
Lost to follow-up	0	0
Protocol violation	1 (2.3)	3 (3.7)
Subject withdrew consent	0	2 (2.5)
Unsatisfactory therapeutic effect	2 (4.5)	10 (12.3)
Study completion		
Completed study	0	0
Discontinued study (withdrawal)	44 (100.0)	81 (100.0)
Main reason for discontinuation of the study		
Administrative problems	43 (97.7)	77 (95.1)
Death	0	1 (1.2)
Lost to follow-up	0	0
Subject withdrew consent	1 (2.3)	3 (3.7)

The percentages are based on the number of randomized patients.

Demographic and Background Characteristics

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

		Tac + MPA n (%)	AEB071 + MPA n (%)
Age (years)	N	44	81
	Mean	48.3	46.4
	Median	47.0	47.0
	SD	13.69	12.30
	Range	20 – 72	20 – 70
Age group (years) – n (%)	<65	39 (88.6)	74 (91.4)
	≥65	5 (11.4)	7 (8.6)
Gender – n (%)	Male	32 (72.7)	49 (60.5)
	Female	12 (27.3)	32 (39.5)
Race – n (%)	Asian	1 (2.3)	5 (6.2)
	Black	2 (4.5)	5 (6.2)
	Caucasian	40 (90.9)	67 (82.7)
	Native American	0	0
	Pacific islander	0	0
	Other	1 (2.3)	4 (4.9)
Weight (kg)	N	42	78
	Mean	80.6	75.0
	Median	77.7	73.2
	SD	15.23	17.86
	Range	48 – 123	44 – 125
End stage disease leading to transplantation – n (%)	Glomerular disease	10 (22.7)	20 (24.7)
	Pyelonephritis	0	2 (2.5)
	Polycystic disease	5 (11.4)	13 (16.0)
	Hypertension / nephrosclerosis	4 (9.1)	9 (11.1)
	Drug induced toxicity	1 (2.3)	1 (1.2)
	Diabetes mellitus	7 (15.9)	6 (7.4)
	Interstitial nephritis	1 (2.3)	2 (2.5)
	Vasculitis	0	1 (1.2)
	Obstructive disorder / reflux	1 (2.3)	3 (3.7)
	Renal hyperplasia / dysplasia	0	0
	IgA nephropathy	0	0
	Unknown	3 (6.8)	7 (8.6)
	Other	12 (27.3)	17 (21.0)
Current dialysis – n (%)	None	10 (22.7)	18 (22.2)
	Hemodialysis	25 (56.8)	51 (63.0)
	Peritoneal dialysis	9 (20.5)	12 (14.8)

Primary Objective Result(s)

Analysis of the composite primary efficacy failure event as well as treated BPAR events up to Month 3 (ITT analysis set, on-treatment)

	Tac + MPA N=44	AEB071 + MPA N=81	Difference AEB071-Tac
Composite efficacy failure			
Number of events	2	16	
K-M failure rate (%)	4.5	25.7	21.2
95% confidence intervals (%)	(0.0, 10.7)	(14.5, 36.9)	(8.4, 34.0)
Treated BPAR			
Number of events	2	14	
K-M failure rate (%)	4.5	23.6	19.1
95% confidence intervals (%)	(0.0, 10.7)	(12.5, 34.8)	(6.4, 31.8)

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 considered 'on-treatment'. The comparison is based on the time up to the middle of the third month (day 104). K-M = Kaplan-Meier, negative differences favor AEB071.

Secondary Objective Result(s)

Tables not available

Safety Results

Number percent of patients reporting AEs (greater or equal to 5 percent in any group) by system organ class and preferred term (Safety analysis set)

	Tac + MPA N=44 n (%)	AEB071 + MPA N=81 n (%)
Total number of patients with AEs	43 (97.7)	79 (97.5)
Total number of patients with SAEs	13 (29.5)	38 (46.9)
Gastrointestinal disorders		
Constipation	10 (22.7)	46 (56.8)
Diarrhea	14 (31.8)	33 (40.7)
Nausea	8 (18.2)	35 (43.2)
Vomiting	6 (13.6)	25 (30.9)
Flatulence	4 (9.1)	6 (7.4)
Dyspepsia	3 (6.8)	5 (6.2)
Abdominal pain	2 (4.5)	5 (6.2)
Metabolism and nutrition disorders		
Hypophosphataemia	9 (20.5)	12 (14.8)
Hypomagnesaemia	11 (25.0)	7 (8.6)
Hypokalaemia	5 (11.4)	10 (12.3)
Hyperglycaemia	4 (9.1)	10 (12.3)
Hyperkalaemia	6 (13.6)	7 (8.6)
Hypocalcaemia	3 (6.8)	9 (11.1)
Diabetes mellitus	3 (6.8)	2 (2.5)
Nervous system disorders		
Dizziness	5 (11.4)	12 (14.8)
Tremor	9 (20.5)	6 (7.4)
Headache	7 (15.9)	5 (6.2)
Dysgeusia	0	11 (13.6)
General disorders and administration site conditions		
Oedema peripheral	9 (20.5)	12 (14.8)
Oedema	4 (9.1)	5 (6.2)
Pyrexia	2 (4.5)	5 (6.2)
Injury, poisoning and procedural complications		
Procedural pain	9 (20.5)	16 (19.8)
Wound complication	3 (6.8)	3 (3.7)
Perinephric collection	3 (6.8)	1 (1.2)
Blood and lymphatic system disorders		
Anaemia	6 (13.6)	16 (19.8)
Leukopenia	3 (6.8)	5 (6.2)
Leukocytosis	3 (6.8)	3 (3.7)
Infections and infestations		
Urinary tract infection	10 (22.7)	16 (19.8)
Nasopharyngitis	3 (6.8)	4 (4.9)

Psychiatric disorders		
Insomnia	7 (15.9)	21 (25.9)
Anxiety	3 (6.8)	3 (3.7)
Investigations		
Blood creatinine increased	8 (18.2)	8 (9.9)
Liver function test abnormal	3 (6.8)	1 (1.2)
White blood cell count increased	3 (6.8)	1 (1.2)
Renal and urinary disorders		
Dysuria	6 (13.6)	8 (9.9)
Haematuria	2 (4.5)	7 (8.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	3 (6.8)	6 (7.4)
Cough	4 (9.1)	3 (3.7)
Pharyngolaryngeal pain	1 (2.3)	5 (6.2)
Vascular disorders		
Hypotension	5 (11.4)	6 (7.4)
Hypertension	3 (6.8)	5 (6.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (11.4)	3 (3.7)
Pain in extremity	4 (9.1)	4 (4.9)
Neck pain	3 (6.8)	0
Cardiac disorders		
Tachycardia	2 (4.5)	8 (9.9)
Immune system disorders		
Kidney transplant rejection	1 (2.3)	6 (7.4)
Skin and subcutaneous tissue disorders		
Acne	4 (9.1)	2 (2.5)

A patient with multiple occurrences of a single 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 dose of study medication.

MedDRA system organ classes and preferred terms are listed by frequency.

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

	Tac + MPA N=44 n (%)	AEB071 + MPA N=81 n (%)
Constipation	10 (22.7)	46 (56.8)
Diarrhea	14 (31.8)	33 (40.7)
Nausea	8 (18.2)	35 (43.2)
Vomiting	6 (13.6)	25 (30.9)
Procedural pain	9 (20.5)	16 (19.8)
Urinary tract infection	10 (22.7)	16 (19.8)
Anaemia	6 (13.6)	16 (19.8)
Oedema peripheral	9 (20.5)	12 (14.8)
Hypophosphataemia	9 (20.5)	12 (14.8)
Insomnia	7(15.9)	21 (25.9)

Serious Adverse Events and Deaths

Number percent of patients who died, had other serious or clinically significant AEs or discontinued because of them (Safety analysis set)

Number percent of patients who died, had other serious or clinically significant AEs or discontinued because of them (Safety analysis set)	Tac + MPA N=44 n (%)	AEB071 + MPA N=81 n (%)
Death	0	1 (1.2)
SAE(s)	13 (29.5)	38 (46.9)
Clinically significant AE(s)/infection(s)	16 (36.4)	42 (51.9)
- Discontinued study medication due to AE(s)/infection(s)	2 (4.5)	18 (22.2)
- Dose reduction/interruption due to AE(s)/infection(s)	14 (31.8)	33 (40.7)

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

Other Relevant Findings

None

Date of Clinical Trial Report 15 May 2009
Date Inclusion on Novartis Clinical Trial Results Database December 2, 2009
Date of Latest Update