NOVARTIS

Sponsor Novartis
Generic Drug Name Sotrastaurin (AEB071)
Therapeutic Area of Trial Liver transplantation
Approved Indication None
Protocol Number CAEB071B2201
Title A 24-month randomized, multicenter study, evaluating efficacy, safety, tolerability and pharmacokinetics of sotrastaurin (STN) combined with tacrolimus (TAC) *vs* a tacrolimus/mycophenolate mofetil (MMF)-based control regimen in *de novo* liver transplant recipients
Phase of Development Phase II
Study Start/End Dates 29-Apr-2010 to 26-Jul-2012 **Early termination date**: 14-Mar-2012 (recruitment was put on hold) **Reason for termination**: Insufficient therapeutic benefit of AEB071 compared to standard of care immunosuppression
Study Design/Methodology This was a multicenter, parallel-group, partially-blinded, randomized study designed to compare the efficacy of sotrastaurin (AEB) based regimens (AEB 200mg/TAC standard group, AEB 200mg/TAC reduced group, AEB 300mg/TAC reduced group) against a control group of tacrolimus (TAC) + Mycophenolate mofetil (MMF) in the prevention of the composite end point of tBPAR (treated biopsy proven acute rejection), graft loss or death; and would possibly provide evidence for improved renal function in the post-transplant period. This study was planned to explore several AEB-based regimens, including a calcineurin inhibitor (CNI) free maintenance regimen with AEB + corticosteroids at Month 6, to find the favorable risk-benefit

profile in liver transplantation recipients. The study consisted of four cohorts and patients were randomized in a 1:1:1:1 ratio.

When approximately 60 patients reached Month 6, an independent Data Monitoring Committee (DMC) recommended that TAC should no longer be withdrawn at Month 6 due to increased acute rejections seen following withdrawal of TAC. They also recommended that those patients that had TAC withdrawn and were maintained on AEB + corticosteroids (CS) should have TAC reintroduced. Based on these recommendations, the protocol was amended to allow patients in Arm 4 to continue on their AEB + TAC regimen without discontinuing TAC at Month 6.

Centers

36 centers in 12 countries: Argentina, Austria, Belgium, Canada, Switzerland, Czech Republic, Germany, Spain, Finland, France, Italy, United States

Publication

None

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

The test drug sotrastaurin (AEB)

- AEB (open-label supplies): 100 mg hard gelatin capsules in yellow opaque color for oral administration of a 200 mg bid dose. These capsules were supplied in bottles (Type 1 bottle).
- AEB (blinded supplies): 100 mg capsules in pink opaque color packaged in a second type of bottle (Type 2 bottle) that was clearly distinct from the Type 1 bottle.
- Matching placebo (blinded supplies): capsules in pink opaque color that are identical in appearance to the corresponding AEB 100 mg capsules packaged in the Type 2 bottle.

The patient received 200 mg bid open-label supplies and either an additional AEB 100 mg bid or placebo (blinded supplies), to achieve a total dose of either 300 mg bid or 200 mg bid.

Statistical Methods

Primary efficacy: The primary efficacy variable was the composite endpoint "primary efficacy failure", defined as tBPAR of Banff grade ≥1, graft loss, or death. The date of efficacy failure was calculated as the earliest date among the 3 types of events. The primary efficacy failure rates were estimated for each treatment arm with the Kaplan-Meier (K-M) product-limit formula. Greenwood's formula was used to estimate the variance of the estimated failure rates and to derive the two-sided 95% normal distribution approximation based confidence intervals (CI) for the difference in failure rates between each AEB arm and the control arm at Month 6 (Day 180).

For each AEB arm, non-inferiority compared to the control arm was tested at Month 6 (Day 180) using a non-inferiority margin of 10%. No adjustment for multiplicity testing was done as the goal of the study was to evaluate and not to choose between proposed AEB regimens.

As supportive analyses, each AEB group was compared with the control group using a logrank test. Furthermore, the primary efficacy analysis was repeated assuming that patients who were lost to follow-up did experience primary efficacy failure at the earliest date for which the information on the primary efficacy variable was missing.

K-M analyses for secondary efficacy variables consisted of K-M estimates of failure rates at selected time points Month 3 (Day 90), Month 6 (Day 180), Month 9 (Day 270), Month 12 (Day 360), corresponding 95% CIs, estimates of differences in failure rates between each AEB arm and control arm with corresponding 95% CIs, and K-M survival/failure curves (excluding death and graft loss). This analysis was also performed for the primary efficacy variable. In addition, maximum severity of first and all BPAR (biopsy proven acute rejection) episodes; frequency of acute rejection episodes and type and treatment of BPAR episodes were summarized. All analyses involving BPAR were based on the acute rejection rating obtained from the local pathologist.

All efficacy analyses used the Full Analysis Set.

Safety and tolerability was assessed by statistical and/or clinical review of all safety parameters including renal safety, AEs/infections, SAE, notable events, cytomegalovirus events, new onset diabetes mellitus (NODM), laboratory tests, ECG assessments and vital signs. All safety analyses used the Safety Set.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

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

- Patients who provided written informed consent and were willing to adhere to the study regimen
- Male and female patients of any race
- Age ≥ 18 years
- *De novo* recipients of a primary orthotopic liver transplant from a deceased donor

Exclusion Criteria

Recipient criteria:

- Prior organ/cellular transplants or of multiple organ transplants
- Anti-HIV-positive. Laboratory results obtained within 6 months prior to transplantation were accepted
- AB0 incompatible allograft
- MELD-score > 35 within 1 month prior transplantation
- Serum creatinine of ≥ 3.0 mg/dL (≥ 265 µmol/L) or on renal replacement therapy for > 1 week

Donor criteria:

- Donor age < 12 years
- Partial (split) liver allograft
- Living donor liver transplantation
- Cardiac death donors (DCD) / non-heartbeating donors
- HIV-positive donors
- HbsAg-positive donors
- Cold ischemic time of >15 hours
- Macrosteatosis > 50%

Medical history & concomitant disease criteria of recipient:

- Acute liver failure (UNOS I, T1)
- Hepatocellular carcinoma (HCC) that exceeded the Milan criteria (1 nodule ≤ 5 cm, 2-3 nodules all ≤ 3 cm) at the time of transplantation
- Past or present malignancy within the past 5 years (other than excised basal cell carcinoma and HCC satisfying the Milan criteria)
- Patients with a condition unsafe to perform biopsy (e.g. coagulopathy without the option of transjugular biopsy)
- Severe active infection considered by the investigator to be unsafe for the study

(Co)medication related criteria:

- Patients with antibody induction or who received any other immunosuppressive therapy not defined in the protocol
- History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer
- Patients who required administration of strongly interacting drugs of the cytochrome P450 3A4 system

Cardiac safety criteria:

- Patients requiring drugs with QT-prolonging properties (e.g. antiarrhythmic drugs, such as

amiodarone, sotalol, dofetilide, quinidine, procainamide, disopyramide)

- Patients with QTc > 470 msec (females) and > 450 msec (males), respectively, at screening or at baseline (Fridericia correction), long QT-syndrome (own or with a family history) or with a family history of sudden unexplained cardiac death
- Patients with left branch bundle block (LBBB) or who experienced, during the previous 6 months, hospitalization for heart failure of cardiac etiology, or significant and persistent 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, or atrial fibrillation or flutter
- Patients with symptomatic coronary artery disease

Participant Flow

Patient disposition (Full analysis set)

	AEB 200mg/ TAC standard N=49 n (%)	AEB 200mg/ TAC reduced N=51 n (%)	AEB 300mg/ TAC reduced N=49 n (%)	MMF/TAC standard N=51 n (%)	Total N=200 n (%)
Study medication					
Discontinued at/after study termination (1)	23 (46.9)	36 (70.6)	26 (53.1)	36 (70.6)	121 (60.5)
Discontinued before study termination	26 (53.1)	15 (29.4)	23 (46.9)	15 (29.4)	79 (39.5)
Main reason for discontinuation before study termination					
Adverse Event(s)	17 (34.7)	10 (19.6)	14 (28.6)	10 (19.6)	51 (25.5)
Unsatisfactory therapeutic effect	0 (0.0)	3 (5.9)	3 (6.1)	1 (2.0)	7 (3.5)
Death	2 (4.1)	1 (2.0)	3 (6.1)	1 (2.0)	7 (3.5)
Subject withdrew consent	2 (4.1)	1 (2.0)	1 (2.0)	0 (0.0)	4 (2.0)
Protocol deviation	3 (6.1)	0 (0.0)	1 (2.0)	0 (0.0)	4 (2.0)
Abnormal laboratory value(s)	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)	2 (1.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	2 (1.0)
Graft loss	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (1.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retransplantation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study					
Discontinued at/after study termination (1)	39 (79.6)	45 (88.2)	39 (79.6)	46 (90.2)	169 (84.5)
Discontinued before study termination	10 (20.4)	6 (11.8)	10 (20.4)	5 (9.8)	31 (15.5)
Main reason for discontinuation before study termination					

Death	9 (18.4)	3 (5.9)	6 (12.2)	3 (5.9)	21 (10.5)
Subject withdrew consent	0 (0.0)	2 (3.9)	2 (4.1)	1 (2.0)	5 (2.5)
Administrative problems	1 (2.0)	1 (2.0)	1 (2.0)	0 (0.0)	3 (1.5)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)	2 (1.0)
Followed up until Month 6 (2)	31 (63.3)	38 (74.5)	35 (71.4)	38 (74.5)	-
Followed up until Month 12 (2)	15 (30.6)	20 (39.2)	18 (36.7)	21 (41.2)	-
Treated until Month 6	19 (38.8)	27 (52.9)	23 (46.9)	26 (51.0)	-
Treated until Month 12	11 (22.4)	15 (29.4)	10 (20.4)	11 (21.6)	-

(1) Only including patients who stopped due to study termination on/after 27 March 2012 (date of study termination). Patients who stopped on/after 27 March 2012 for other reasons are included below.

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

(2) Indicates efficacy follow up until Month 6 and 12

Baseline Characteristics

Recipient demographics and viral status by treatment group (Full analysis set)

		AEB 200mg/ TAC standard N=49	AEB 200mg/ TAC reduced N=51	AEB 300mg/ TAC reduced N=49	MMF/TAC standard N=51
Age (years)	N	49	51	49	51
	Mean (SD)	56.4 (8.44)	53.8 (11.34)	55.1 (8.86)	53.3 (10.20)
	Median	58.0	55.0	57.0	55.0
	Range (Min, Max)	30, 68	18, 68	34, 70	19, 74
Age group- n (%)	< 65	44 (89.8)	45 (88.2)	41 (83.7)	46 (90.2)
	>= 65	5 (10.2)	6 (11.8)	8 (16.3)	5 (9.8)
Gender- n (%)	Male	37 (75.5)	39 (76.5)	33 (67.3)	27 (52.9)
	Female	12 (24.5)	12 (23.5)	16 (32.7)	24 (47.1)
Race- n (%)	Caucasian	45 (91.8)	45 (88.2)	48 (98.0)	45 (88.2)
	Black	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
	Asian	2 (4.1)	1 (2.0)	0 (0.0)	1 (2.0)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	2 (4.1)	4 (7.8)	1 (2.0)	5 (9.8)
Weight (kg)	N	46	47	46	49
	Mean (SD)	79.3 (16.01)	80.6 (15.63)	82.2 (21.48)	74.4 (14.23)
	Median	77.5	79.0	77.4	75.9
	Range (Min, Max)	54 , 129	56 , 129	51 , 125	42 , 105
Viral status- n (%)	CMV Positive	28 (57.1)	28 (54.9)	34 (69.4)	35 (68.6)
	EBV Positive	39 (79.6)	42 (82.4)	41 (83.7)	41 (80.4)
	HCV Positive	0 (0.0)	2 (3.9)	1 (2.0)	2 (3.9)
	HBsAg Positive	8 (16.3)	10 (19.6)	3 (6.1)	4 (7.8)
	Anti-Hep B Surface Positive	8 (16.3)	12 (23.5)	15 (30.6)	10 (19.6)

	Anti-Hep B Core Positive	8 (16.3)	9 (17.6)	5 (10.2)	6 (11.8)

Donor-related background characteristics

		AEB 200mg/ TAC standard N=49	AEB 200mg/ TAC reduced N=51	AEB 300mg/ TAC reduced N=49	MMF/TAC standard N=51
Age (years)	Mean (SD)	60.8 (16.21)	52.8 (18.61)	53.5 (17.34)	57.6 (15.01)
	Median	65.0	53.0	54.0	57.0
	Range (Min , Max)	18 , 83	15 , 88	13 , 87	19 , 83
Age group - n (%)	< 50	11 (22.4)	20 (39.2)	20 (40.8)	15 (29.4)
	>= 50	38 (77.6)	31 (60.8)	29 (59.2)	36 (70.6)
Gender - n (%)	Male	24 (49.0)	28 (54.9)	25 (51.0)	32 (62.7)
	Female	25 (51.0)	23 (45.1)	24 (49.0)	19 (37.3)
Race - n (%)	Caucasian	16 (32.7)	21 (41.2)	17 (34.7)	22 (43.1)
	Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	29 (59.2)	23 (45.1)	26 (53.1)	23 (45.1)
	Other	4 (8.2)	7 (13.7)	5 (10.2)	6 (11.8)
Viral status - n (%)	CMV Positive	27 (55.1)	31 (60.8)	29 (59.2)	36 (70.6)
	EBV Positive	23 (46.9)	28 (54.9)	19 (38.8)	26 (51.0)
	HCV Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	HBsAg Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Anti-Hep B Surface Positive	2 (4.1)	5 (9.8)	5 (10.2)	6 (11.8)
	Anti-Hep B Core Positive	3 (6.1)	1 (2.0)	2 (4.1)	4 (7.8)
	HIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Donor status – n (%)	Deceased heart beating	49 (100.0)	51 (100.0)	49 (100.0)	51 (100.0)
Type of transplant	Whole liver	48 (98.0)	51 (100.0)	49 (100.0)	51 (100.0)
– n (%)	Split liver	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension –n (%)		7 (14.3)	4 (7.8)	8 (16.3)	7 (13.7)
Cause of death – n	Traumatic	9 (18.4)	7 (13.7)	12 (24.5)	9 (17.6)
(%)	Hypoxia	3 (6.1	4 (7.8)	1 (2.0)	4 (7.8)
	Cerebrovascular event	31 (63.3)	29 (76.5)	35 (71.4)	37 (72.5)
	Other	6 (12.2)	1 (2.0)	1 (2.0)	1 (2.0)
ABO match – n	Identical	44 (89.9)	38 (74.5)	41 (83.7)	41 (80.4)
(%)	Compatible	5 (10.2)	13 (25.5)	8 (16.3)	10 (19.6)
Cold ischemia time	0 to 5 h	12 (24.5)	10 (19.6)	11 (22.4)	4 (7.8)

classified – n (%)	> 5 to 10 h	28 (57.1)	32 (62.7)	28 (57.1)	43 (84.3)
	> 10 to 15 h	9 (18.4)	9 (17.6)	9 (18.4)	3 (5.9)
	> 15 h	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)

Outcome measures

Primary objective: To evaluate the incidence of primary efficacy failure (defined as a composite efficacy endpoint of treated biopsy-proven acute rejection (tBPAR) of Banff Grade ≥ 1 episodes, graft loss, or death) for each AEB arm relative to the control arm in *de novo* liver transplant patients at Month 6 post transplantation.

Secondary objectives:

Main safety objective was to:

- Evaluate renal function (estimated Glomerular Filtration Rate, abbreviated MDRD formula 4 [$eGFR_{MDRD}$]) in each AEB arm relative to the control arm at Month 12.

Other secondary objectives were to:

- Evaluate the incidence of the primary efficacy failure for each AEB arm relative to the control arm at Months 3, 12, and 24, and evaluate the components of the primary efficacy endpoint (tBPAR, graft loss, death) at Months 3, 6, 12, and 24, respectively.
- Evaluate the incidence of composite secondary efficacy failures defined as tBPAR of Banff Grade ≥ 1 episodes that are steroid-resistant, acute rejections requiring T-cell depleting treatment, graft loss or death) for each AEB arm relative to the control arm at Months 3, 6, 12 and 24.
- Evaluate the incidence of tBPAR of Banff Grade ≥ 1 episodes that are steroid-resistant, and, separately, of all acute rejections that require T-cell depleting treatment, for each AEB arm relative to the control arm at Months 3, 6, 12 and 24.
- Evaluate renal function for each AEB arm relative to the control arm at Months 3, 6, 12 and 24 (values and change from Month 1) using different methods such as abbreviated MDRD-4, cystatin C-based Hoek formula, serum creatinine, calculated creatinine clearance (Cockcroft-Gault formula), quantitative protein/creatinine ratio (for proteinuria).
- Evaluate the overall safety in different treatment arms as rated by the incidence of AEs and SAEs at Months 3, 6, 12 and 24.
- Evaluate the tolerability in the different treatment arms as rated by the incidence of premature discontinuation, dose reduction or interruption of study drugs at Months 3, 6, 12 and 24.
- Evaluate incidence of new onset diabetes (NODM) for each AEB arm relative to the control arm at Months 6, 12 and 24.
- Characterize the pharmacokinetics of AEB over time post-transplant and explore dose-exposure and exposure-response relationships.

Primary Outcome Result(s)

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

	AEB 200mg/ TAC standard N=49	AEB 200mg/ TAC reduced N=51	AEB 300mg/ TAC reduced N=49	MMF/TAC standard N=51
Composite efficacy failure at Day 180				
Number of events	12	8	10	8
K-M failure rate (%)	25.0	16.5	20.9	15.9
95% confidence interval (%)	(12.7, 37.2)	(6.0, 27.0)	(9.3, 32.4)	(5.8, 26.0)
Difference AEB - control at Day 180				
K-M failure rate (%)	9.1	0.6	5.0	-
95% confidence interval (%)	(-6.8, 25.0)	(-14.0, 15.2)	(-10.3, 20.3)	-
Non-inferiority shown	No	No	No	-

Composite efficacy failure: tBPAR of Banff grade >=1, graft loss, or death. The analysis also includes events with onset after discontinuation of study medication.

K-M = Kaplan-Meier; negative differences favor AEB.

Confidence intervals were calculated using the normal distribution approximation for K-M failure rates.

The hypothesis 'AEB is not more than 10% worse than control (MMF/TAC standard)' was tested.

Non-inferiority was shown if the upper limit of the 95% CI of difference to control was lower than 10%.

Secondary Outcome Result(s)

Analysis of estimated GFR (MDRD) at selected time points (safety set)

Visit window / Treatment group	Observed value (mL/min/SA)						Comparison of AEB groups with MMF/TACst		
	n	Mean	SD	Median	Min	Max	Diff	P val	95% CI
Day 1									
AEB 200mg/TACst	42	97.8	41.85	93.8	34.3	182.0	11.7	0.209	-5.4, 28.1
AEB 200mg/TACred	47	89.4	35.48	88.1	32.3	175.7	4.5	0.553	-9.7, 20.0
AEB 300mg/TACred	37	88.8	32.23	77.0	32.0	165.6	3.3	0.621	-10.5, 18.7
MMF/TACst	42	84.6	32.56	78.9	30.8	154.0			
Month 6									
AEB 200mg/TACst	22	88.0	31.11	87.4	39.2	152.6	8.3	0.325	-8.9, 28.3
AEB 200mg/TACred	26	86.3	23.75	82.9	48.6	145.3	7.8	0.383	-8.6, 24.5
AEB 300mg/TACred	24	89.1	19.24	88.8	47.6	121.2	10.9	0.163	-3.9, 27.4
MMF/TACst	27	77.7	30.59	81.1	20.1	136.3			
Month 12									
AEB 200mg/TACst	11	83.8	19.91	86.9	54.6	124.8	-0.9	0.784	-18.3, 20.6
AEB 200mg/TACred	17	88.2	19.11	87.0	63.3	129.7	4.3	0.471	-12.6, 21.2
AEB 300mg/TACred	11	77.8	21.77	73.1	52.0	125.4	-6.7	0.450	-27.8, 10.6
MMF/TACst	12	83.7	20.33	87.8	51.5	119.4			
Month 18									
AEB 200mg/TACst	1	51.6		51.6	51.6	51.6	-10.0	1.000	-27.5, 7.5
AEB 200mg/TACred	6	88.8	30.90	79.1	62.5	143.4	22.9	0.432	-16.7, 99.3

AEB 300mg/TACred	0					
MMF/TACst	2	61.6	24.79	61.6	44.1	79.1

Diff = Hodges-Lehmann estimate

The hypothesis of no difference between AEB and control group was tested using the Wilcoxon-Mann-Whitney test.

95% confidence intervals for the location shift (AEB - MMF/TACst) were calculated based on Hodges-Lehmann estimates.

Multiple measurements within a visit window other than baseline are averaged.

Analysis of time to treated BPAR at Month 6 (Full analysis set)

	AEB 200mg/ TAC_{st} N=49	**AEB 200mg/ TAC_{red} N=51**	**AEB 300mg/ TAC_{red} N=49**	**MMF/TAC_{st} N=51**
Treated BPAR (Banff >= 1)				
Number of events	5	4	5	6
K-M failure rate (%)	10.5	8.0	11.3	12.1
95% confidence interval (%)	(1.8, 19.3)	(0.5, 15.5)	(1.9, 20.7)	(3.0, 21.1)
Difference AEB - control at Day 180				
K-M failure rate (%)	-1.5	-4.1	-0.8	-
95% confidence interval (%)	(-14.1, 11.1)	(-15.8, 7.7)	(-13.8, 12.3)	-

Events with onset after discontinuation of study medication are included in the analysis.

K-M = Kaplan-Meier; negative differences favor AEB.

Confidence intervals were calculated using the normal distribution approximation for K-M failure rates.

Analysis of time to graft loss at Month 6 (Full analysis set)

	AEB 200mg/ TAC_{st} N=49	**AEB 200mg/ TAC_{red} N=51**	**AEB 300mg/ TAC_{red} N=49**	**MMF/TAC_{st} N=51**
Graft loss				
Number of events	3	1	3	2
K-M failure rate (%)	6.5	2.0	6.2	3.9
95% confidence interval (%)	(0.0, 13.7)	(0.0, 5.8)	(0.0, 13.0)	(0.0, 9.2)
Difference AEB - control at Day 180				
K-M failure rate (%)	2.6	-2.0	2.3	-
95% confidence interval (%)	(-6.3, 11.5)	(-8.5, 4.6)	(-6.4, 10.9)	-

Graft loss: need for re-transplantation or death due to liver failure

Events with onset after discontinuation of study medication are included in the analysis.

K-M = Kaplan-Meier; negative differences favor AEB.

Confidence intervals were calculated using the normal distribution approximation for K-M failure rates.

Analysis of time to death at Month 6 (Full analysis set)

	AEB 200mg/ TAC_{st} N=49	AEB 200mg/ TAC_{red} N=51	AEB 300mg/ TAC_{red} N=49	MMF/TAC_{st} N=51
Death				
Number of deaths	7	3	5	1
K-M death rate (%)	15.2	6.7	10.7	2.0
95% confidence interval (%)	(4.8, 25.7)	(0.0, 14.1)	(1.8, 19.7)	(0.0, 5.8)
Difference AEB - control at Day 180				
K-M death rate (%)	13.3	4.8	8.8	-
95% confidence interval (%)	(2.2, 24.4)	(-3.5, 13.1)	(-0.9, 18.5)	-

Deaths after discontinuation of study medication are included in the analysis.

K-M = Kaplan-Meier; negative differences favor AEB.

Confidence intervals were calculated using the normal distribution approximation for K-M death rates.

Analysis of time to graft loss or death at Month 6 Full analysis set)

	AEB 200mg/ TAC_{st} N=49	AEB 200mg/ TAC_{red} N=51	AEB 300mg/ TAC_{red} N=49	MMF/TAC_{st} N=51
Graft loss or death				
Number of events	8	4	7	2
K-M failure rate (%)	16.7	8.6	14.7	3.9
95% confidence interval (%)	(6.1, 27.3)	(0.5, 16.6)	(4.6, 24.9)	(0.0, 9.2)
Difference AEB - control at Day 180				
K-M failure rate (%)	12.8	4.6	10.8	-
95% confidence interval (%)	(1.0, 24.6)	(-5.0, 14.3)	(-0.6, 22.3)	-

Graft loss: need for re-transplantation or death due to liver failure

Events with onset after discontinuation of study medication are included in the analysis.

K-M = Kaplan-Meier; negative differences favor AEB.

Confidence intervals were calculated using the normal distribution approximation for K-M failure rates.

Safety Results

Adverse Events by System Organ Class

Adverse events by primary system organ class - number (%) of patients (Safety set)

	AEB 200mg/ TAC standard N=48 n (%)	AEB 200mg/ TAC reduced N=53 n (%)	AEB 300mg/ TAC reduced N=45 n (%)	MMF/TAC standard N=52 n (%)
Total number of patients with any AE	47 (97.9)	51 (96.2)	45 (100.0)	51 (98.1)
Primary system organ class				
Gastrointestinal disorders	38 (79.2)	33 (62.3)	41 (91.1)	40 (76.9)
Infections and infestations	30 (62.5)	26 (49.1)	31 (68.9)	32 (61.5)
Metabolism and nutrition disorders	35 (72.9)	34 (64.2)	31 (68.9)	32 (61.5)
Injury, poisoning and procedural complications	24 (50.0)	28 (52.8)	26 (57.8)	25 (48.1)
Investigations	16 (33.3)	25 (47.2)	25 (55.6)	20 (38.5)
Renal and urinary disorders	26 (54.2)	20 (37.7)	24 (53.3)	22 (42.3)
Nervous system disorders	21 (43.8)	20 (37.7)	23 (51.1)	20 (38.5)
General disorders and administration site conditions	22 (45.8)	27 (50.9)	22 (48.9)	32 (61.5)
Blood and lymphatic system disorders	21 (43.8)	19 (35.8)	20 (44.4)	31 (59.6)
Respiratory, thoracic and mediastinal disorders	21 (43.8)	25 (47.2)	20 (44.4)	19 (36.5)
Psychiatric disorders	23 (47.9)	23 (43.4)	19 (42.2)	18 (34.6)
Cardiac disorders	21 (43.8)	19 (35.8)	17 (37.8)	10 (19.2)
Vascular disorders	18 (37.5)	24 (45.3)	17 (37.8)	24 (46.2)
Hepatobiliary disorders	23 (47.9)	25 (47.2)	16 (35.6)	19 (36.5)
Musculoskeletal and connective tissue disorders	15 (31.3)	16 (30.2)	15 (33.3)	17 (32.7)
Skin and subcutaneous tissue disorders	14 (29.2)	16 (30.2)	13 (28.9)	12 (23.1)
Immune system disorders	5 (10.4)	5 (9.4)	6 (13.3)	2 (3.8)
Reproductive system and breast disorders	3 (6.3)	4 (7.5)	6 (13.3)	2 (3.8)
Ear and labyrinth disorders	3 (6.3)	6 (11.3)	5 (11.1)	2 (3.8)
Eye disorders	3 (6.3)	3 (5.7)	5 (11.1)	1 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (12.5)	5 (9.4)	2 (4.4)	3 (5.8)
Congenital, familial and genetic disorders	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	2 (4.2)	1 (1.9)	0 (0.0)	0 (0.0)
Social circumstances	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)

MedDRA system organ classes are sorted by descending frequency in the AEB 300 mg/TAC reduced group.

A patient with multiple AEs in different system organ classes is only counted once per organ class.

SAEs occuring more than 30 days and non-serious AEs occurring more than 7 days after last study medication are excluded.

Infections are considered special AEs and are therefore included in the summary.

MedDRA Version 15.1 was used for coding.

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

Most frequent AEs (>= 10% in any group) by preferred term - number (%) of patients (Safety set)

	AEB 200mg/ TAC standard N=48 n (%)	AEB 200mg/ TAC reduced N=53 n (%)	AEB 300mg/ TAC reduced N=45 n (%)	MMF/TAC standard N=52 n (%)
Total number of patients with any AE	47 (97.9)	51 (96.2)	45 (100.0)	51 (98.1)
Preferred term				
Nausea	13 (27.1)	17 (32.1)	22 (48.9)	12 (23.1)
Vomiting	15 (31.3)	14 (26.4)	19 (42.2)	13 (25.0)
Anaemia	12 (25.0)	13 (24.5)	17 (37.8)	11 (21.2)
Diarrhoea	9 (18.8)	20 (37.7)	16 (35.6)	11 (21.2)
Constipation	16 (33.3)	15 (28.3)	15 (33.3)	11 (21.2)
Insomnia	13 (27.1)	12 (22.6)	14 (31.1)	7 (13.5)
Pleural effusion	12 (25.0)	13 (24.5)	13 (28.9)	10 (19.2)
Abdominal pain	13 (27.1)	13 (24.5)	12 (26.7)	16 (30.8)
Hypertension	11 (22.9)	19 (35.8)	12 (26.7)	16 (30.8)
Back pain	6 (12.5)	9 (17.0)	10 (22.2)	8 (15.4)
Cholestasis	9 (18.8)	10 (18.9)	9 (20.0)	10 (19.2)
Cytomegalovirus infection	4 (8.3)	5 (9.4)	9 (20.0)	3 (5.8)
Tremor	6 (12.5)	2 (3.8)	9 (20.0)	10 (19.2)
Cholangitis	8 (16.7)	10 (18.9)	8 (17.8)	3 (5.8)
Oedema peripheral	10 (20.8)	9 (17.0)	8 (17.8)	6 (11.5)
Renal failure acute	6 (12.5)	6 (11.3)	8 (17.8)	5 (9.6)
Renal impairment	8 (16.7)	4 (7.5)	8 (17.8)	3 (5.8)
Urinary tract infection	8 (16.7)	5 (9.4)	8 (17.8)	7 (13.5)
Headache	10 (20.8)	7 (13.2)	7 (15.6)	8 (15.4)
Hypokalaemia	5 (10.4)	6 (11.3)	7 (15.6)	2 (3.8)
Hypomagnesaemia	8 (16.7)	7 (13.2)	7 (15.6)	4 (7.7)
Wound complication	3 (6.3)	2 (3.8)	7 (15.6)	6 (11.5)
Diabetes mellitus	7 (14.6)	4 (7.5)	6 (13.3)	3 (5.8)
Hepatic enzyme increased	2 (4.2)	5 (9.4)	6 (13.3)	6 (11.5)
Hypoalbuminaemia	5 (10.4)	5 (9.4)	6 (13.3)	5 (9.6)
Leukopenia	3 (6.3)	4 (7.5)	6 (13.3)	14 (26.9)
Renal failure	7 (14.6)	8 (15.1)	6 (13.3)	11 (21.2)
Bile duct stenosis	4 (8.3)	4 (7.5)	5 (11.1)	1 (1.9)
Dyspnoea	3 (6.3)	4 (7.5)	5 (11.1)	3 (5.8)
Flatulence	3 (6.3)	4 (7.5)	5 (11.1)	4 (7.7)
Hypocalcaemia	2 (4.2)	3 (5.7)	5 (11.1)	1 (1.9)
Hypophosphataemia	4 (8.3)	8 (15.1)	5 (11.1)	3 (5.8)

Procedural pain	8 (16.7)	13 (24.5)	5 (11.1)	4 (7.7)
Pyrexia	13 (27.1)	12 (22.6)	5 (11.1)	16 (30.8)
Electrocardiogram QT prolonged	5 (10.4)	1 (1.9)	4 (8.9)	0 (0.0)
Hyperglycaemia	7 (14.6)	11 (20.8)	4 (8.9)	7 (13.5)
Oliguria	5 (10.4)	2 (3.8)	4 (8.9)	2 (3.8)
Pruritus	7 (14.6)	9 (17.0)	4 (8.9)	5 (9.6)
Sinus tachycardia	6 (12.5)	3 (5.7)	4 (8.9)	1 (1.9)
Tachycardia	8 (16.7)	7 (13.2)	4 (8.9)	1 (1.9)
Hyperkalaemia	10 (20.8)	4 (7.5)	3 (6.7)	9 (17.3)
Nasopharyngitis	5 (10.4)	7 (13.2)	2 (4.4)	6 (11.5)
Pneumonia	9 (18.8)	1 (1.9)	2 (4.4)	5 (9.6)
Thrombocytopenia	8 (16.7)	2 (3.8)	2 (4.4)	9 (17.3)
Chills	5 (10.4)	3 (5.7)	1 (2.2)	3 (5.8)
Haemoglobin decreased	3 (6.3)	7 (13.2)	1 (2.2)	1 (1.9)
Hypotension	4 (8.3)	1 (1.9)	1 (2.2)	7 (13.5)
Leukocytosis	6 (12.5)	3 (5.7)	0 (0.0)	4 (7.7)

MedDRA preferred terms are sorted by descending frequency in the AEB 300 mg/TAC reduced group.

A patient with multiple AEs is only counted once per preferred term.

SAEs occuring more than 30 days and non-serious AEs occurring more than 7 days after last study medication are excluded. Infections are considered special AEs and are therefore included in the summary.

MedDRA Version 15.1 was used for coding.

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious adverse events, or had events leading to discontinuation of study medication (Safety set)

	AEB 200mg/ TAC standard N=48 n (%)	AEB 200mg/ TAC reduced N=53 n (%)	AEB 300mg/ TAC reduced N=45 n (%)	MMF/TAC standard N=52 n (%)
Death	9 (18.8)	3 (5.7)	5 (11.1)	3 (5.8)
<= 30 days of discontinuation of study medication	5 (10.4)	1 (1.9)	4 (8.9)	1 (1.9)
> 30 days after discontinuation of study medication	4 (8.3)	2 (3.8)	1 (2.2)	2 (3.8)
SAE(s)	34 (70.8)	33 (62.3)	31 (68.9)	27 (51.9)
AE(s) leading to discontinuation of study medication	21 (43.8)	12 (22.6)	13 (28.9)	12 (23.1)
SAE(s) leading to discontinuation of study medication	17 (35.4)	7 (13.2)	7 (15.6)	7 (13.5)
Non-serious AE(s) leading to discontinuation of study medication	5 (10.4)	5 (9.4)	6 (13.3)	5 (9.6)
AE(s) leading to dose adjustment or interruption	21 (43.8)	18 (34.0)	15 (33.3)	32 (61.5)
SAE(s) leading to dose adjustment or interruption	6 (12.5)	4 (7.5)	8 (17.8)	8 (15.4)
Non-serious AE(s) leading to dose adjustment or interruption	16 (33.3)	14 (26.4)	12 (26.7)	28 (53.8)

SAEs occurring more than 30 days after last study medication and non-serious AEs occurring more than 7 days after last study medication are excluded. Infections are considered special AEs and are therefore included in the summary.

Other Relevant Findings

Increased acute rejections following withdrawal of Tacrolimus at month 6

Date of Clinical Trial Report

18-Feb-2013

Date Inclusion on Novartis Clinical Trial Results Database

23-May-2013

Date of Latest Update

02-May-2013