Sponsor

Novartis

Generic Drug Name

AEB071 (sotrastaurin)

Therapeutic Area of Trial

Liver transplantation

Approved Indication

Investigational

Study Number

CAEB071B2101

Title

An open-label, two-period, multi-center, single dose study to assess the pharmacokinetics of AEB071 in *de novo* liver transplant patients

Phase of Development

Phase I

Study Start/End Dates

03 Oct 2007 / 17 Feb 2008

Study Design/Methodology

Multicenter, multinational, open-label, two single dose, two-period, safety, tolerability and pharmacokinetics of study of AEB071 in liver transplant patients.
Following orthotopic liver transplantation, patients were enrolled to receive two single doses of 100 mg AEB071 in two distinct periods during their first two weeks post transplant.

Centres

3 centers in 3 countries: Germany (1), Italy (1), Switzerland (1).

Publication

No publication.

Objectives

Primary objective

- Pharmacokinetics of AEB071and primary metabolite, N-desmethyl AEB071, in liver transplant patients in the immediate post transplant period

Secondary objective(s)

- Pharmacokinetics of tacrolimus in the presence of AEB071
- Safety and tolerability of AEB071 in liver transplant patients
- Biliary excretion of AEB071and primary metabolite, N-desmethyl AEB071, from patients with a T-tube.
- Relationship of free drug concentration, α-1 acid glycoprotein concentration and pharmacokinetics of AEB071

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

Oral capsules of AEB071 100mg, single dose in each period. Study medication was administered in one of two ways, per a nasogastric tube (NG-tube) or orally as a capsule.

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

As this study was designed to determine AEB071 pharmacokinetics in *de novo* liver transplant patients, a standard immunosuppressive regimen of tacrolimus (FK506, Prograf®) and/or MPA with or without steroids was maintained in all patients as per local practice.

Criteria for Evaluation

Primary variables

- PK variables derived for AEB071 and N-desmethyl AEB071: AUC0-t, AUC0-inf, Cmax

Secondary variables

- PK variables derived for AEB071 and N-desmethyl AEB071: tmax, T1/2, CL/F, CLbiliary
- PK variables derived for tacrolimus in the presence of AEB071: AUC0-t, AUC0-inf, Cmax

Safety and tolerability

- Adverse events, serious adverse events, ECG, vital signs, standard lab variables

Pharmacology

- Biliary excretion of AEB071and primary metabolite, N-desmethyl AEB071, from patients with a T-tube
- Relationship of free drug concentration, α-1-acid glycoprotein concentration and pharmacokinetics of AEB071

Other

N/A

Statistical Methods

All subjects who received at least one treatment were included in the safety and tolerability evaluation.

All subjects with quantifiable pharmacokinetic (PK) measurements were included in the pharmacokinetic data analysis.

- Primary variables
  - Primary PK variables were log-transformed and analyzed using a mixed effects linear model. Period was included in the model as a fixed effect and subject as a random effect.
  - Means and 90% confidence intervals were computed for each period on the transformed scale and back transformed to provide geometric means and corresponding 90% confidence intervals for each period.
- Secondary variables: descriptive statistics

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male and female patients of any race, 18 years or older
- Primary orthotopic liver transplant recipients.
- Allograft functioning at an acceptable level by 24 hrs as determined by local investigator
- Recipients initiated on tacrolimus and/or MPA therapy (within 12 hours of transplantation).
- Females capable of becoming pregnant have a negative pregnancy test within 7 days prior to enrollment.

Exclusion criteria

- Recipients of prior organ transplants or patients recipients of multiple organ transplants (including combined liver-kidney transplantation).
- Recipients of ABO incompatible transplants.
- Recipients of living donor transplants or split liver transplants
- Transplant with a cold ischemic time (CIT) of >12 hours.
- Transplants of donors after cardiac death (DCD).
- Patients with a MELD-score >35 during 1 month prior transplantation
- Transplant of a marginal graft into a patient with a MELD-score > 28 defined by any of the following criteria: donor age > 60, CIT > 10h, hypotension periods or inotropic support of the donor, stay on ICU > 3 days, graft steatosis > 30%
- Patients with acute, fulminant hepatic failure (UNOS I, T1)
- Patients with any past or present malignancy (other than excised basal cell carcinoma and hepato-cellular carcinoma (HCC).
- Patients with a serum creatinine > 4.0 mg/dL or on dialysis
- Patients who have received or are expected to receive induction antibody or any other immunosuppressive therapy not defined in the protocol.
- Existence of any surgical or medical condition, other than the current transplant, which, in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of the study medication.

Number of Subjects

	Novartis product
Planned N	12
Randomized n	13
Intent-to-treat population (ITT) n (%)	13
Completed n (%)	12
Withdrawn n (%)	1
Withdrawn due to adverse events n (%)	1
Withdrawn due to lack of efficacy n (%)	0
Withdrawn for other reasons n (%)	0

Demographic and Background Characteristics

	Novartis product
N (ITT)	13
Females : males	5 : 8
Mean age, years (SD)	57.2 (7)
Mean weight, kg (SD)	84.8 (16)
Race Caucasian n (%) Black n (%) Asian n (%) Other n (%)	 13 (100.0 %) 0 (0.0%) 0 (0.0%) 0 (0.0%)

Primary Objective Result(s) – Summary statistics

Primary PK analysis

	AEB071		**N-desmethyl AEB071**	
PK parameter	Period 1	Period 2	Period 1	Period 2
C_{max} (ng/mL)	530 ± 480	631 ± 471	14.5 ± 7.6	12.6 ± 7.3
AUC_{0-t} (h.ng/mL)	3481 ± 1435	3848 ± 3230	137 ± 134	102 ± 197

Secondary Objective Result(s)

AEB071 pharmacokinetics based on free (unbound) drug in blood. In the first post-transplant week, patients tended to have higher plasma levels of the AEB071 binding protein a1-acid-glycoprotein. This was associated with AUC based on free drug in blood at the lower end of the healthy subject range or below.
AEB071 excretion in externally-drained bile. Biliary clearance of intact AEB071 was negligible consistent with the fact that the parent drug is extensively metabolized with little unchanged drug remaining for excretion.
Tacrolimus pharmacokinetics. Tacrolimus exposure was in the expected range implying that any acute pharmacokinetic influence of AEB071 on tacrolimus was not apparent under the study conditions.

Safety Results

Adverse Events by System Organ Class

	AEB071 N (%)
Patients studied	
Randomized patients	13 (100)
Patients with drug-related AE	N/A
AEs occurring in more than 10% (n>1) of the patients	
Gastrointestinal disorders	6 (46.2)
General disorders and administration site conditions	2 (15.4)
Hepatobiliary disorders	6 (46.2)
Immune system disorders	6 (46.2)
Infections and infestations	4 (30.8)
Investigations	3 (23.1)
Metabolism and nutrition disorders	6 (46.2)
Musculoskeletal and connective tissue disorders	2 (15.4)
Nervous system disorders	3 (23.1)
Psychiatric disorders	5 (38.5)
Renal and urinary disorders	2 (15.4)
Respiratory, thoracic and mediastinal disorders	3 (23.1)
Vascular disorders	2 (15.4)

10 AEs occurring in more than 10% (n>1) of the patients by Preferred Term n (%)

AE	AEB071
Constipation	2 (15.4)
Cholangitis	6 (46.2)
Diarrhea	2 (15.4)
Pyrexia	2 (15.4)
Liver transplant rejection	5 (38.5)
Urinary Tract infection	3 (23.1)
Hypokalaemia	2 (15.4)
Insomnia	5 (38.5)
Pleural effusion	2 (15.4)
Hypotension	2 (15.4)

Serious Adverse Events and Deaths

	Novartis product
No. (%) of subjects studied	13 (100)
No. (%) of subjects with AE(s)	13 (100)
Number (%) of subjects with serious or other significant events	n (%)
Death	0 (0)
SAE(s)	5 (35.5)
Discontinued due to SAE(s)	1 (7.7)

None of the SAEs occurring in this study were suspected to be drug related.

Other Relevant Findings

N/A

Date of Clinical Trial Report

21-June-2010

Date Inclusion on Novartis Clinical Trial Results Database:

31-Mar-2009

Date of Latest Update:

17-Feb-2009


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