Sponsor

Novartis

Generic Drug Name

Sotrastaurin

Trial Indication(s)

Not Applicable

Protocol Number

CAEB071A2117

Protocol Title

A two part, randomized, placebo controlled study to evaluate the pharmacokinetics and cardiovascular pharmacodynamics of AEB071 in combination with ritonavir in healthy volunteers

Clinical Trial Phase

Phase I

Study Start/End Dates

11 Feb 2008 to 29 Dec 2008

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

Part I was an open-label, single-treatment study in which subjects received 300 mg ritonavir the evening of day 1 and, 12 hours later in the morning of day 2, 300 mg ritonavir with 100 mg AEB071. Pharmacokinetics of AEB071 with ritonavir were compared to historical data of AEB071 alone. Part II was a partially-blinded, randomized, placebo-controlled, 4-treatment, 4-period, crossover study. The dose of ritonavir was 300 mg; the dose of AEB071 was 500 mg; and the placebo matched AEB071 in appearance (there was no ritonavir placebo). Subjects received the following 4 treatments day1 (evening)/day2 (morning): (1) placebo/placebo, (2) ritonavir + placebo/ritonavir + placebo (3) placebo/AEB071, (4) ritonavir + placebo/AEB071 + ritonavir.

Centers

France (1)

Objectives:

Primary Objective:

- Part I. The objective was to explore the tolerability and pharmacokinetics of 100 mg AEB071 in combination with the strong CYP3A4 inhibitor ritonavir.
- Part II. The primary objective was to evaluate the tolerability and pharmacokinetics of supratherapeutic AEB071 exposure following a single oral dose of AEB071 administered with the strong CYP3A4 inhibitor ritonavir.

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

Single oral dose of 100 mg capsule of AEB071 in Part I and 500 mg capsule of AEB071 in Part II was administered.

Statistical Methods

Linear mixed model for pharmacokinetic parameters between treatments and linear mixed-effects models on electrocardiogram QT intervals and heart rate for cardiovascular responses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Healthy male or female subjects age 18 to 45 years of age included, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.

Exclusion criteria

- A marked baseline prolongation of QT/QTcF interval (e.g., repeated demonstration of a QTcF interval >500);
- A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);
- Presence of clinically significant illness, active infectious process (viral or bacterial) including (but not limited to) history of herpetic infections, positive tuberculosis tests, other infections at risk of relapse or documented drug allergies that may affect the subject's safety during the study.
- Laboratory or clinical evidence suggestive of liver or renal disease, history of heart disease, history of autonomic dysfunction (e.g. history of fainting, orthostatic hypotension, sinus arrhythmia), history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated), history major gastrointestinal disease, history or clinical evidence of pancreatic injury or pancreatitis.
- Subjects with a resting heart rate < 40 bpm or > 90 bpm
- Subjects with systolic blood pressure < 90 or diastolic blood pressure < 50 mmHg.
- Subjects with lymphocyte counts less than 1000/mm^3 or total WBC greater than 11000/mm^3 at baseline
- Subject who intend to or have received any live attenuated vaccines 4 weeks prior to or during the study period.
- History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

Participant Flow Table

Subject disposition Part I Safety analysis set

Disposition Reason	300 mg ritonavir + 100 mg AEB071 N=12
Completed	12 (100.0)

Subject disposition Part II Safety analysis set

Disposition Reason	Overall N=31
Completed	27 (87.1)
Discontinued	4 (12.9)
Subject withdrew consent	4 (12.9)

Baseline Characteristics

Summary of demographic information Part I Safety analysis set

Demographic Variable	300 mg ritonavir + 100 mg AEB071 N=12
Age (years)	
n	12
mean	27.8
SD	7.01
minimum	19
median	28.5
maximum	39
Height (cm)	
n	12
mean	174.5
SD	4.56
minimum	167
median	175.0
maximum	182
Weight (kg)	
n	12
mean	67.58
SD	5.351
minimum	56.0
median	68.50
maximum	74.0
BMI (kg/m2)	
n	12
mean	22.225
SD	2.0105
minimum	19.25
median	22.370
maximum	25.91

Summary of demographic information Part II Safety analysis set

Demographic Variable	Sequence A N=7	Sequence B N=8	Sequence C N=8	Sequence D N=8	All Subjects N=31
Age (years)					
n	7	8	8	8	31
mean	33.3	27.0	25.0	30.3	28.7
SD	9.48	7.11	7.76	9.88	8.75
minimum	21	19	18	19	18
median	36.0	24.0	23.0	28.0	25.0
maximum	44	36	42	44	44
Height (cm)					
n	7	8	8	8	31
mean	171.1	176.9	176.8	177.3	175.6
SD	5.73	6.27	2.38	9.30	6.59
minimum	166	166	174	165	165
median	168.0	177.5	177.0	175.0	175.0
maximum	179	183	180	192	192
Weight (kg)					
n	7	8	8	8	31
mean	63.71	71.25	67.50	70.25	68.32
SD	5.376	8.548	8.281	11.235	8.757
minimum	60.0	60.0	57.0	54.0	54.0
median	62.00	69.50	65.50	69.50	66.00
maximum	75.0	84.0	82.0	90.0	90.0
BMI (kg/m2)					
n	7	8	8	8	31
mean	21.793	22.706	21.585	22.224	22.086
SD	2.0713	1.5791	2.4011	1.7329	1.9184
minimum	19.35	20.76	18.83	19.83	18.83
median	21.260	22.215	20.555	21.795	21.770
maximum	25.35	25.08	26.17	25.01	26.17

Sex					
Male	7 (100.0 %)	8 (100.0 %)	8 (100.0 %)	8 (100.0 %)	31 (100.0 %)
Predominant Race					
Caucasian	6 (85.7 %)	7 (87.5 %)	7 (87.5 %)	7 (87.5 %)	27 (87.1 %)
Black	1 (14.3 %)	1 (12.5 %)		1 (12.5 %)	3 (9.7 %)
Asian			1 (12.5 %)		1 (3.2 %)
Ethnicity					
Other	7 (100.0 %)	8 (100.0 %)	8 (100.0 %)	8 (100.0 %)	31 (100.0 %)

Treatment sequence: A = 300 mg ritonavir + 500 mg AEB071 / Placebo / 500mg AEB071 / 300mg ritonavir + Placebo B = Placebo / 500mg AEB071 / 300mg ritonavir + Placebo / 300 mg ritonavir + 500 mg AEB071 C = 500mg AEB071 / 300mg ritonavir + Placebo / 300 mg ritonavir + 500 mg AEB071 / Placebo D = 300mg ritonavir + Placebo / 300 mg ritonavir + 500 mg AEB071 / Placebo / 500mg AEB071 Note: Weight and height are taken from Screening Vital Signs evaluations.

Summary of Efficacy

Primary Outcome Result:

AEB071 pharmacokinetics: study part I

Parameter	Study 2117 100 mg AEB071 + ritonavir	Historical studies 100 mg AEB071 alone
N	12	43
AEB071:		
Tmax (h)	4 (1 – 6)	1 (0.5 – 4)
Cmax (ng/ml)	786 ± 275	551 ± 245
AUClast (ng.h/ml)	10421 ± 3121	3115 ± 1385
AUCinf (ng.h/ml)	10508 ± 3113	3264 ± 1463
T1/2 (h)	7.7 ± 1.0	6.0 ± 0.9
N-desmethyl-AEB071:		
Tmax (h)	5 (2 – 10)	1.5 (0.5 – 4)
Cmax (ng/ml)	24 ± 6	23 ± 8
AUClast (ng.h/ml)	409 ± 91	116 ± 44

Values are mean ± sd except for Tmax which is median (range).

AEB071 pharmacokinetics: study part II

Parameter	500 mg AEB071 alone	500 mg AEB071 + ritonavir	Geometric mean ratio (90%CI)
AEB071:			
Tmax (h)	4 (1 – 6)	6 (2 – 10)	--
Cmax (ng/ml)	1560 ± 517	2287 ± 557	1.53 (1.36, 1.71)
AUClast (ng.h/ml)	17917 ± 5909	44072 ± 13438	2.47 (2.13, 2.87)
AUCinf (ng.h/ml)	17981 ± 5917	44259 ± 13530	2.47 (2.13, 2.87)
CL/F (l/h)	31 ± 11	13 ± 7	--
Vz/F (l)	300 ± 109	158 ± 82	--
T1/2 (h)	6.7 ± 1.1	8.6 ± 0.8	1.30 (1.25, 1.34)
N-desmethyl-AEB071:			
Tmax (h)	3 (1 – 6)	6 (3 – 16)	--
Cmax (ng/ml)	65 ± 30	91 ± 30	1.46 (1.27, 1.67)
AUClast (ng.h/ml)	750 ± 247	2351 ± 761	3.12 (2.64, 3.69)
AUCinf (ng.h/ml)	814 ± 244	2451 ± 769	2.98 (2.55, 3.48)
T1/2 (h)	11.1 ± 1.5	14.2 ± 1.2	1.29 (1.24, 1.35)
Metabolic ratio	0.044 ± 0.011	0.058 ± 0.013	--

Values are mean ± sd except for Tmax which is median (range). 90%CI = 90% confidence interval.

Refer to Safety Result section for the tolerability part of the primary outcome result.

Summary of Safety

Safety Results

Subjects with adverse events by body system and preferred term Part I Safety analysis set

Body system Preferred Term	300 mg ritonavir + 100 mg AEB071 N=12 n (%)
-Any Body System	
-TOTAL	2 (16.7)
Gastrointestinal disorders	
-TOTAL	1 (8.3)
Vomiting	1 (8.3)
General disorders and administration site conditions	
-TOTAL	1 (8.3)
Malaise	1 (8.3)
Vascular disorders	
-TOTAL	1 (8.3)
Orthostatic hypotension	1 (8.3)

Under one treatment,
A subject with multiple occurrences of an adverse event is only counted once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied n = number of subjects with at least one AE in that category
Only adverse events occurring at or after first drug intake are included

Adverse events in study part II by preferred term with incidence >5%

Most frequent adverse events* by preferred term	AEB071 + ritonavir N=30 n(%)	Placebo N=29 n(%)	AEB071 N=29 n(%)	Ritonavir N=29 n(%)
Total number of subjects with AEs	28 (93.3)	6 (20.7)	20 (69.0)	9 (31)
Cardiac disorders				
Palpitations	1 (3.3)	–	–	–
Gastrointestinal disorders				
Abdominal pain	7 (23.3)	–	3 (10.3)	–
Diarrhea	2 (6.7)	1 (3.4)	1 (3.4)	1 (3.4)
Nausea	11 (36.7)	–	4 (13.8)	1 (3.4)
Vomiting	6 (20)	–	–	2 (6.9)
General disorders and administration site conditions				
Aesthenia	1 (3.3)	–	2 (6.9)	–
Malaise	2 (6.7)	–	–	–
Nervous system disorders				
Dizziness	2 (6.7)	–	–	–
Dizziness postural	2 (6.7)	–	–	–
Dysgeusia	4 (13.3)	–	1 (3.4)	2 (6.9)
Headache	11 (36.7)	2 (6.9)	2 (6.9)	1 (3.4)
Presyncope	3 (10)	2 (6.9)	-	1 (3.4)
Renal and urinary disorders				
Chromaturia	15 (50)	1 (3.4)	15 (51.7)	1 (3.4)
Vascular disorders				
Hypotension	1 (3.3)	–	–	–
Orthostatic hypotension	5 (16.7)	–	–	1 (3.4)
Eye disorders				
Photopsia	7 (23.3)	–	1 (3.4)	–
Vision blurred	1 (3.3)			

*Truncated AEs include: flatulence, abdominal pain upper, tinnitus, dry mouth, food poisoning, hypoaesthesia oral, lip oedema, stomach discomfort, dysuria, oropharyngeal pain, hyperhydrosis, ingrowing nail, hot flush, vision blurred. AEs truncated at < 5% incidence (n >1) unless otherwise specified

Serious Adverse Events and Deaths

No subjects experienced SAEs and no deaths were reported.

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report

30 Jun 2010