Sponsor

Novartis

Generic Drug Name

Sotrastaurin

Trial Indication(s)

CD79-mutant diffuse large B-cell lymphoma

Protocol Number

COEB071X2101

Protocol Title

An Open-Label, Single-arm, Phase I study of AEB071 (a Protein Kinase C Inhibitor) in Patients with CD79-mutant Diffuse Large B-Cell Lymphoma

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

17-Nov-2011 to 02-Apr-2014

Reason for Termination (If applicable)

Due to challenging enrollment and availability of other treatment options for patients with diffuse large B-cell lymphoma, the study was terminated early and the dose expansion phase was not conducted.

Study Design/Methodology

This was an open-label, multicenter, Phase I study comprised of a dose escalation phase and a dose expansion phase.

Centers

France (3), Germany (1), Korea (1), Taiwan (1), United Kingdom (1), United States (3)

Publication

None

Objectives:

Primary Objectives

- To estimate the maximum tolerated dose (MTD) of sotrastaurin in patients with diffuse large B-cell lymphoma (DLBCL)
- To characterize the safety and tolerability of the MTD or recommended Phase 2 dose (RP2D) of sotrastaurin in patients with DLBCL

Key Secondary Objectives

- To assess the overall response rate (partial response [PR] + complete response [CR]) to sotrastaurin
- To further characterize the safety and tolerability of sotrastaurin

Other Secondary Objectives

- To evaluate single- and multiple-dose pharmacokinetics (PK) of sotrastaurin in patients with DLBCL
- To assess the pharmacodynamic (PD) response to sotrastaurin in lymphoma and blood specimens

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

Sotrastaurin tablets at dose strengths of 50 mg, 100 mg, and 300 mg were administered orally.

Statistical Methods

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, WHO/ECOG performance status, medical conditions, etc., were listed, and were summarized by treatment group using standard descriptive statistics and/or contingency tables (qualitative data). The CD79 mutational status was listed. Disease history was summarized and listed. Relevant medical history and current medical conditions were listed by treatment group. Prior anti-neoplastic medications were summarized and listed, and other prior anti-neoplastic therapies were listed.

Estimation of the MTD during the dose escalation phase of the study was based upon the estimation of the posterior distribution of the probability of dose-limiting toxicity (DLT) in Cycle 1 (28 days) in patients in the Dose-Determining Set (DDS). An adaptive Bayesian logistic regression model (with 2 parameters) guided by the escalation with overdose control (EWOC) principle was used to make dose recommendations and estimate the MTD during the dose escalation phase of the study.

Efficacy for all patients was evaluated by the Investigator using the non-Hodgkin Lymphoma International Working Group response criteria based on contrast-enhanced CT. Summary tables were provided of best overall response by treatment group. This summary also included

the overall response rate (ORR) (PR + CR) in response to sotrastaurin by treatment group. The ORR with 95% confidence interval was calculated, and the Full Analysis Set (FAS) was used.

All safety analyses were based on the Safety Set. The only exceptions were the summaries of DLTs for which the DDS was used. Reports on safety included all AEs, SAEs, and the regular monitoring of laboratory evaluations, physical examination, vital signs, weight, performance status evaluation and ECGs. Total dose, dose intensity, and relative dose intensity of sotrastaurin were summarized. Dose administration record by treatment group was listed for the Safety Set.

PK parameters (including Tmax, Cmax, and AUC0-8h) were determined for both sotrastaurin and its active metabolite AEE800 on PK profiles after the first dose and at steady-state (Cycle 1 Day 8) using non-compartmental method(s).

The cytokine data were listed by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

- The patient population was comprised of adult patients with DLBCL who had mutations in CD79A or CD79B and had experienced relapse following anthracycline-based chemotherapy and autologous bone marrow or stem cell transplant (non-transplant eligible patients may have been considered for the study following chemotherapy alone). Patients were to have Word Health Organization (WHO) performance status of ≤2.
- Key exclusion criteria included severe systemic infections, a known history of human immunodeficiency virus, impaired cardiac function or clinically significant cardiac diseases, treatment with strong inducers or inhibitors of CYP3A4 that could not be discontinued, and a known history of active hepatitis B or C infection unless receiving antiviral therapy.

Participant Flow Table

Patient disposition by treatment group (Full Analysis Set)

	Sotrastaurin 300 mg bid N=4 n (%)	Sotrastaurin 450 mg bid N=8 n (%)	Sotrastaurin 550 mg bid N=3 n (%)	All patients N=15 n (%)
Patients treated				
Treatment discontinued	4 (100)	8 (100)	3 (100)	15 (100)
Primary reason for end of treatment				
Adverse Event(s)	1 (25.0)	0	1 (33.3)	2 (13.3)
Patient withdrew consent	1 (25.0)	2 (25.0)	0	3 (20.0)
Disease progression	2 (50.0)	5 (62.5)	2 (66.7)	9 (60.0)

	Sotrastaurin 300 mg bid N=4 n (%)	Sotrastaurin 450 mg bid N=8 n (%)	Sotrastaurin 550 mg bid N=3 n (%)	All patients N=15 n (%)
Protocol deviation	0	1 (12.5)	0	1 (6.7)
Primary reason for study evaluation completion				
Patient withdrew consent	1 (25.0)	2 (25.0)	0	3 (20.0)
Death	1 (25.0)	1 (12.5)[a]	1 (33.3)	3 (20.0)[a]
Follow-up phase completed as per protocol	2 (50.0)	4 (50.0)	2 (66.7)	8 (53.3)

a: One additional death occurred within the follow-up period after the patient withdrew consent leading to a total of 4 deaths. The death information is not reported in the data listings but is included in the ARGUS report and in a narrative.

Baseline Characteristics

Demographics by treatment group (Full Analysis Set)

	Sotrastaurin 300 mg bid N=4	Sotrastaurin 450 mg bid N=8	Sotrastaurin 550 mg bid N=3	All patients N=15
Age (Years, at screening)				
n	4	8	3	15
Mean (SD)	68.3 (24.10)	66.3 (11.02)	77.3 (6.03)	69.0 (14.48)
Median	77.0	63.5	78.0	72.0
Min-Max	33.0-86.0	52.0-84.0	71.0-83.0	33.0-86.0
Age category (Years, at screening) n (%)				
<65	1 (25.0)	4 (50.0)	0	5 (33.3)
≥65	3 (75.0)	4 (50.0)	3 (100)	10 (66.7)
Sex n (%)				
Male	1 (25.0)	4 (50.0)	1 (33.3)	6 (40.0)
Female	3 (75.0)	4 (50.0)	2 (66.7)	9 (60.0)
Predominant Race n (%)				
Caucasian	3 (75.0)	7 (87.5)	2 (66.7)	12 (80.0)
Asian	1 (25.0)	0	1 (33.3)	2 (13.3)
Other	0	1 (12.5)	0	1 (6.7)
Ethnicity -n (%)				
Hispanic/Latino	0	0	1 (33.3)	1 (6.7)
Chinese	1 (25.0)	0	0	1 (6.7)
Japanese	1 (25.0)	0	0	1 (6.7)
Other	2 (50.0)	8 (100)	2 (66.7)	12 (80.0)

	Sotrastaurin 300 mg bid N=4	Sotrastaurin 450 mg bid N=8	Sotrastaurin 550 mg bid N=3	All patients N=15
WHO performance status[a] n (%)				
0	2 (50.0)	1 (12.5)	0	3 (20.0)
1	2 (50.0)	4 (50.0)	3 (100)	9 (60.0)
2	0	2 (25.0)	0	2 (13.3)
Missing	0	1 (12.5)	0	1 (6.7)

a: 0 - Fully active, able to carry on all pre-disease performance without restriction;
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair;
5 – Dead
bid = twice daily.

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of best overall disease response as per Investigator assessment by treatment group (Full Analysis Set)

	Sotrastaurin 300 mg bid N=4 n (%)	Sotrastaurin 450 mg bid N=8 n (%)	Sotrastaurin 550 mg bid N=3 n (%)	All patients N=15 n (%)
Best overall response[a]				
Complete response (CR)	1 (25.0)	0 (0.0)	1 (33.3)	2 (13.3)
Partial response (PR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)
Progressive disease (PD)	0 (0.0)	4 (50.0)	1 (33.3)	5 (33.3)
Unknown	2 (50.0)	4 (50.0)	1 (33.3)	7 (46.7)
Overall response rate (ORR)[b] (CR or PR)	1 (25.0)	0 (0.0)	1 (33.3)	2 (13.3)
95% CI	(0.6-80.6)	(0.0-36.9)	(0.8-90.6)	(1.7-40.5)

a: Best overall response is based on investigator's assessment of disease status using International Working Group criteria.
b: Estimate (95% CI) for ORR was obtained using exact binomial 95% confidence interval test

Summary of Safety

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class (Safety set)

Primary system organ class	Sotrastaurin 250 mg qd N=1 n (%)	Sotrastaurin 300 mg bid N=4 n (%)	Sotrastaurin 450 mg bid N=7 n (%)	Sotrastaurin 550 mg bid N=3 n (%)	All patients N=15 n (%)
Any primary system organ class	1 (100)	4 (100)	7 (100)	3 (100)	15 (100)
Blood and lymphatic system disorders	1 (100)	3 (75.0)	3 (42.9)	0	7 (46.7)
Cardiac disorders	0	1 (25.0)	1 (14.3)	1 (33.3)	3 (20.0)
Eye disorders	0	0	1 (14.3)	1 (33.3)	2 (13.3)
Gastrointestinal disorders	0	4 (100)	6 (85.7)	3 (100)	13 (86.7)
General disorders and administration site conditions	0	4 (100)	2 (28.6)	1 (33.3)	7 (46.7)
Immune system disorders	0	1 (25.0)	0	0	1 (6.7)
Infections and infestations	0	2 (50.0)	0	0	2 (13.3)
Investigations	0	1 (25.0)	1 (14.3)	0	2 (13.3)
Metabolism and nutrition disorders	0	3 (75.0)	4 (57.1)	1 (33.3)	8 (53.3)
Musculoskeletal and connective tissue disorders	0	2 (50.0)	1 (14.3)	0	3 (20.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (25.0)	1 (14.3)	1 (33.3)	3 (20.0)
Nervous system disorders	0	1 (25.0)	4 (57.1)	1 (33.3)	6 (40.0)
Psychiatric disorders	0	2 (50.0)	0	1 (33.3)	3 (20.0)
Renal and urinary disorders	0	0	1 (14.3)	1 (33.3)	2 (13.3)
Respiratory, thoracic and mediastinal disorders	0	2 (50.0)	3 (42.9)	0	5 (33.3)
Skin and subcutaneous tissue disorders	0	2 (50.0)	1 (14.3)	1 (33.3)	4 (26.7)
Vascular disorders	0	1 (25.0)	0	0	1 (6.7)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All patients' column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported.
qd = once daily dosing; bid = twice daily dosing.

Clinical Trial Results Database

Adverse events, regardless of study drug relationship, by preferred term and treatment group (Safety set), with greater than or equal to 10% incidence for all patients

Preferred term	Sotrastaurin 250 mg qd N=1 n (%)	Sotrastaurin 300 mg bid N=4 n (%)	Sotrastaurin 450 mg bid N=7 n (%)	Sotrastaurin 550 mg bid N=3 n (%)	All patients N=15 n (%)
-Total	1 (100)	4 (100)	7 (100)	3 (100)	15 (100)
Nausea	0	3 (75.0)	5 (71.4)	1 (33.3)	9 (60.0)
Diarrhea	0	2 (50.0)	5 (71.4)	1 (33.3)	8 (53.3)
Decreased appetite	0	2 (50.0)	3 (42.9)	1 (33.3)	6 (40.0)
Vomiting	0	3 (75.0)	3 (42.9)	0	6 (40.0)
Anemia	1 (100)	3 (75.0)	0	0	4 (26.7)
Constipation	0	3 (75.0)	0	1 (33.3)	4 (26.7)
Dysgeusia	0	0	3 (42.9)	0	3 (20.0)
Dyspnea	0	2 (50.0)	1 (14.3)	0	3 (20.0)
Fatigue	0	1 (25.0)	1 (14.3)	1 (33.3)	3 (20.0)
Febrile neutropenia	1 (100)	1 (25.0)	1 (14.3)	0	3 (20.0)
Hypercal-cemia	0	0	3 (42.9)	0	3 (20.0)
Insomnia	0	2 (50.0)	0	1 (33.3)	3 (20.0)
Pruritus	0	2 (50.0)	1 (14.3)	0	3 (20.0)
Thrombo-cytopenia	1 (100)	1 (25.0)	1 (14.3)	0	3 (20.0)
Neutropenia	0	0	2 (28.6)	0	2 (13.3)
Rash erythema-tous	0	1 (25.0)	1 (14.3)	0	2 (13.3)
Sinus tachycardia	0	1 (25.0)	1 (14.3)	0	2 (13.3)
Tumor lysis syndrome	0	1 (25.0)	1 (14.3)	0	2 (13.3)
Tumor pain	0	1 (25.0)	0	1 (33.3)	2 (13.3)

Preferred terms are sorted in descending frequency of all grades column, as reported in the 'All patients' column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple AEs is counted only once in the total row.

Only AEs occurring during treatment or within 30 days of the last study medication are rep orted.

qd = once daily dosing; bid = twice daily dosing.

Clinical Trial Results Database

Number of patients who died or experienced other serious or clinically significant adverse events (Safety set)

	Sotrastaurin 250 mg qd	Sotrastaurin 300 mg bid	Sotrastaurin 450 mg bid	Sotrastaurin 550 mg bid	All patients
	N=1	N=4	N=7	N=3	N=15
Type of event	n (%)	n (%)	n (%)	n (%)	n (%)
Death[a]	0	1 (25.0)	1[a] (14.3)	1 (33.3)	3[a] (20.0)
SAEs	1 (100.0)	2 (50.0)	4 (57.1)	1 (33.3)	8 (53.3)
Discontinued due to AEs	0	1 (25.0)	0	0	1 (6.7)
Discontinued due to SAEs	0	0	0	1 (33.3)	1 (6.7)

a: One additional death occurred within the follow-up period after the patient withdrew consent leading to a total of 4 deaths. The death information is not reported in the data listings but is included in the ARGUS report and in a narrative.

Other Relevant Findings

Conclusion:

The primary objective of this study was to determine the maximum tolerated dose (MTD) of single-agent sotrastaurin when administered orally twice daily (bid) in a 28-day cycle to adult patients with relapsed or refractory CD79 mutant diffuse large B-cell lymphoma (DLBCL). As expected from the published literature, the incidence of the CD79 mutation was found to be low, with only 38 patients (14.39%) identified with the CD79 mutation out of 264 total patients with samples analyzed at the central laboratory. The difficulty in identifying patients with the CD79 mutation and the advanced nature of the disease in this patient population led to challenges in enrollment. Due to these challenges and in view of other treatment options available for patients with DLBCL, this study was terminated early. As a result, the MTD was not determined since the number of evaluable patients treated in any cohort was less than 6, and the dose expansion phase was not conducted. The posterior distribution of dose-limiting toxicity rates indicated that doses up to 400 mg bid (800 mg/day) satisfied the escalation with overdose control criteria.

No conclusions could be drawn regarding pharmacodynamics or pharmacokinetics due to the small number of patients and limited data available. Similarly, as only 15 patients were enrolled in the Full Analysis Set/Safety Set, the efficacy and safety data are limited, making it difficult to draw any clinically meaningful conclusions. Overall, the adverse events observed in this study are consistent with the known safety profile for sotrastaurin.

Date of Clinical Trial Report

16-Dec-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

6-Jan-2015

Date of Latest Update

Reason for Update