Sponsor

Novartis

Generic Drug Name

Panobinostat (LBH589)

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Study Number

CLBH589B2110

Title

A Phase IB, study to investigate the effect of ketoconazole, a CYP3A4 inhibitor, on oral panobinostat and to assess the efficacy and safety of oral panobinostat in patients with advanced solid tumors

Phase of Development

Ib

Study Start/End Dates

12 Sep 2007 to 14 Apr 2010

Study Design/Methodology

This was an open-label, multiple-dose, single-sequence crossover drug-drug interaction (DDI) study, with the Core Phase (Days 1 to 14) followed by an Extension Phase (Day 15 onward).
The Core Phase was comprised of a single-dose of 20 mg oral panobinostat (Day 1) followed by multiple doses of ketoconazole 400 mg p.o. (Day 5 to 9) to maximize the potential for CYP3A4 inhibition. On Day 8, a single dose of 20 mg oral panobinostat was given in combination with ketoconazole. No panobinostat was given between Days 8 and 14 to allow complete washout of panobinostat and ketoconazole.
During the Extension Phase oral panobinostat at 20 mg was administered 3 times a week (TIW) every week (QW) on Monday, Wednesday, and Friday (MWF) as a single agent starting on Day 15 of Cycle 1 and as part of 28-day treatment cycles in subsequent cycles.

Centres

2 centers in 2 countries: USA (1), Netherlands (1)

Publication

None

Objectives

Primary objective(s)

To determine the effects of multiple-dose ketoconazole on the pharmacokinetics (PK) of single-dose oral panobinostat in patients with advanced solid tumors (core study).

Secondary objective(s)

- To assess the PK of the final market image (FMI) formulation of panobinostat administered alone on Day 1 (prior to ketoconazole co-administration during the Core Phase).
- To assess the safety and tolerability of oral panobinostat when co-administered with ketoconazole (Core Phase) or without ketoconazole in the Extension Phase.
- To assess the best clinical response of oral panobinostat in patients with advanced solid tumors treated with panobinostat (Extension Phase).
- To explore effects of oral panobinostat on biomarkers of angiogenesis and apoptosis (Extension Phase).
- To explore the effect of CYP3A4/5 polymorphism on panobinostat PK (Core Phase).

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

Oral panobinostat was supplied as 5-mg or 20-mg hard gelatin capsules. Dosing was previously described in the Methodology section. Dosing was on a flat scale of mg/day, and not adjusted for weight or body surface area. Patients were instructed to take the daily dose of oral panobinostat with a glass of water in the morning (at approximately the same time), after a minimum 2-hour fast, and to continue fasting for 2 hours after swallowing the dose of panobinostat. Patients were also instructed to swallow the whole capsules, and should not chew them.Ketoconazole (Nizoral®) was supplied as 200 mg tablets. Ketoconazole was administered as 2 x 200 mg (400 mg) p.o. daily in the morning for a total of 5 doses starting on Day 5. No food was given 2 h before and after ketoconazole administration.

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

N/A

Criteria for Evaluation

Primary variables

- PK parameters e.g. AUC and C_{max} (core phase)

Secondary variables

- Efficacy based on physician's evaluation utilizing RECIST criteria version 1.0 (extension)

Safety and tolerability

- Monitoring and recording all AEs, SAEs, with their severity (evaluated by the CTCAE version 3.0), and assessments of vital signs, performance status (ECOG performance), physical condition, body weight, cardiac evaluations (ECG evaluations), and cardiac imaging.

Pharmacology

Panobinostat PK data

Briefly, blood samples (~3 mL/sample) for panobinostat PK evaluation were collected following 20 mg panobinostat dose at pre-dose and serial timepoints post-dose up to 48 hours on Days 1 (single agent panobinostat) and 8 (combination of ketoconazole and panobinostat) during the first treatment cycle in 14 patients with advanced cancer.

- Day 1 panobinostat PK: pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, and 48 hour post-dose
- Day 8 panobinostat PK: pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, and 48 hour post-dose

Ketoconazole PK data

Two blood samples/day (~3 mL/sample) for ketoconazole PK evaluation were obtained during Cycle 1 Days 5, 8, and 9 following ketoconazole 400 mg o.d. oral dose.

- Day 5, first ketoconazole dose: pre-dose and 2 hour post-dose.
- Day 8, combination treatment and 4th ketoconazole dose: pre-dose and 2 hour post-dose.
- Day 9, fifth ketoconazole dose: pre-dose and 2 hour post-dose.

Other

Biomarker assessments

Genotype status of CYP3A was explored in relationship to panobinostat PK

optional biomarker assessment (apoptosis and angiogenesis) were to be collected at baseline, on Cycle 1 Day 26, at time of confirmation of CR or PR and at end of treatment

Fetal hemoglobin protein level was measured at local sites on Day 1 of every cycle when blood for hematology was drawn for routine safety and efficacy assessments and results were reported together with these analytes.

Statistical Methods

A formal statistical analysis was performed for Cmax, AUC_{0-24}, and AUC_{0-inf} of panobinostat with and without ketoconazole. A linear mixed-effects model was fit to the log-transformed PK parameters. Included in the model was treatment (ketoconazole + panobinostat or panobinostat alone) as fixed effects, and patient as a random effect. The point estimate of the treatment difference and the corresponding 90% confidence intervals (CIs) were calculated and anti-logged to obtain the point estimate and CI on the linear scale for the ratio of geometric means of the test as compared with the reference.

The assessment of safety was based mainly on the frequency and severity of AEs and on the number of laboratory values (hematology and biochemistry) falling outside of pre-determined ranges. Other safety data (e.g., ECG and vital signs) were summarized as appropriate. Response rate based on investigator assessment was evaluated during the Extension Phase.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria:

- Age ≥18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
- Women of childbearing potential (WOCBP) must have had a negative serum pregnancy test within 7 days prior to the administration of the first study treatment.
- Patients with histologically or cytologically confirmed advanced solid tumors whose disease had progressed despite standard therapy or for whom no standard therapy existed.
- Patients with solid tumors should have had at least one measurable and/or non-measurable lesion as defined by RECIST criteria.

Key exclusion criteria:

- Patients with chronic liver toxicity.
- Impairment of gastrointestinal (GI) function, obstruction of GI disease that might significantly alter the absorption of oral panobinostat.
- Any active or uncontrolled severe infections.
- Other concurrent severe and/or uncontrolled medical conditions
- Patients currently receiving chemotherapy, immunotherapy, or radio-therapy or who had received these within 4 weeks of study entry.
- Patients unwilling to or suspected not to comply with the protocol.

Number of Subjects

	Panobinostat
Planned N	24
Intent-to-treat population (ITT) n (%)	14 (100)
End of treatment n (%)	14 (100)
Primary reason for end of treatment	
Adverse events n (%)	3 (21.4)
Disease progression n (%)	10 (71.4)
Death n (%)	1 (7.1)

Demographic and Background Characteristics

	Panobinostat
N (ITT)	14
Females : males	5:9
Mean age, years (SD)	59.4 (10.43)
Mean weight, kg (SD)	80.1 (15.71)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 14 (100) 0 (0) 0 (0) 0 (0)
Characteristics relevant to study population	BMI: 27.0 (2.80) BSA (m^2): 1.9 (0.25)

Primary Objective Result(s)

Mean (CV%) of panobinostat PK parameters following an oral dose of 20 mg panobinostat (PAN) (Day 1) and in combination with 400 mg of ketoconazole (Keto) (Day 8)

	Day 1 PAN alone	Day 8 PAN + Keto
T_{max} (hr)#	1 [0.5-4] (n=14)	1 [0.5-6] (n=14)
C_{max} (ng/mL)	20 (36%) (n=14)	40 (80%) (n=14)
AUC_{0-24} (ng*hr/mL)	111 (32%) (n=14)	188 (56%) (n=14)
AUC_{0-inf} (ng*hr/mL)	140 (34%) (n=13)	249 (52%) (n=12)
$T_{1/2}$(h)	12.1 (35%) (n=13)	12.8 (31%) (n=13)
#median [range].		

Statistical analysis of primary PK parameters of panobinostat

				Treatment Comparison			
					90% CI		
PK Parameter	**Treatment**	**n***	**Adjusted**	**Comp.**	**Geo-mean**	**Low-er**	**Up-per**
			Geo-mean		**Ratio**		
C_{max} (ng/mL)	Pano alone	14	18.5				
	Pano + Keto	14	30.0	Test:Ref	1.62	1.211	2.166
AUC_{0-inf} (ng.h/mL)	Pano alone	11	126.0				
	Pano + Keto	12	224.0	Test:Ref	1.78	1.451	2.177
T_{max} (h)	Pano alone	14	1.00				
	Pano + Keto	14	1.00	Test-Ref	0.00	-2.50	3.00

Treatment group: Test: panobinostat + ketoconazole; Reference: panobinostat alone.

n* = number of patients with non-missing values; Geo-mean = geometric mean. Geo-mean, Geo-mean ratio, and 90% CI are determined from mixed effect model and back-transformed from log scale.

The model on log transformed PK parameters includes treatment (Keto + panobinostat or panobinostat alone) as fixed effect, and patient as a random effect. For Tmax, median was presented under "Geo-Mean", median of difference (Test-Reference) under "Geo-mean ratio", min and max difference under "Lower" and "Upper".

Secondary Objective Result(s)

Genotyping results

Genotyping analysis of CYP3A4*1B, CYP3A5*2, *3, *6 and *7 was performed in all 14 patients. Wild type allele CYP3A4*1A is defined as the exclusion of allele CYP3A4*1B. Wild type allele CYP3A5*1 is defined as the exclusion of alleles *2, *3, *6 and *7.

All patients in this study were Caucasians. Fourteen patients had homozygous wild-type CYP3A4*1A genotype. Eleven patients had homozygous CYP3A5*3 genotype and 3 patients had heterozygous CYP3A5*1/*3 genotype. The table below shows panobinostat PK parameters in the 3 patients who carried heterozygous CYP3A5*1/*3 alleles. There is no apparent difference in panobinostat C_{max} or AUC values between patients carrying CYP3A5*1/*3 and CYP3A5*3/*3 alleles.

Day 1 C_{max} and AUC values of patients with heterozygous CYP3A5*1/*3 genotype

Patient Number	**C_{max} (ng/mL)**	**AUC_{0-24} (ng*hr/mL)**
A	32.2	172
B	24	117
C	12.7	70
Median (range) C_{max} in patients with CYP3A5*3/*3: 19.1 (7.1-28.6) ng/mL.		
Median (range) AUC_{0-24} in patients with CYP3A5*3/*3: 115 (67-158) ng*hr/mL.		

Biomarker results

Fetal hemoglobin was collected at local sites on Day 1 of every cycle. Change from baseline by visit was presented for the safety set and listing presented for FAS, together with apoptosis biomarkers. There appears to be a trend of induction of fetal hemoglobin levels after panobinostat

treatment. Compared to baseline, M30/M65 ratio as an indicator of apoptosis level remains globally unchanged at the end of Cycle 1 (Day 26 after treatment started). An increase in the levels of angiogenesis markers, bFGF, PLGF, sVEGFR1, and VEGF at the end of Cycle 1 was observed as compared to baseline.

Overall, the limited sample size does not allow meaningful conclusions to be drawn from these data.

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and period (preferred term occurring in at least 10% of the patients) – core phase (Safety set)

Primary System Organ Class **Preferred Term**	**Period 1** **N=14** **n (%)**	**Period 2** **N=14** **n (%)**	**Period 3** **N=14** **n (%)**	**All Patients** **N=14** **n (%)**
-**Any primary system organ class**				
-Total	10 (71.4)	8 (57.1)	9 (64.3)	12 (85.7)
Gastrointestinal disorders				
-Total	7 (50.0)	2 (14.3)	7 (50.0)	10 (71.4)
Diarrhea	2 (14.3)	0 (0.0)	4 (28.6)	5 (35.7)
Vomiting	4 (28.6)	0 (0.0)	1 (7.1)	4 (28.6)
Nausea	2 (14.3)	1 (7.1)	2 (14.3)	3 (21.4)
General disorders and administration site condi-tions				
-Total	3(21.4)	2 (14.3)	1 (7.1)	5 (35.7)
Fatigue	2(14.3)	0 (0.0)	1 (7.1)	2 (14.3)
Metabolism and nutrition disorders				
-Total	2 (14.3)	3(21.4)	4(28.6)	8 (57.1)
Anorexia	2 (14.3)	2 (14.3)	0 (0.0)	4 (28.6)
Hypophosphataemia	0 (0.0)	1 (7.1)	3 (21.4)	3 (21.4)
Hypocalcaemia	0 (0.0)	0 (0.0)	2 (14.3)	2 (14.3)
Musculoskeletal and con-nective tissue disorders				
-Total	1 (7.1)	2 (14.3)	3 (21.4)	5 (35.7)
Myalgia	0 (0.0)	2 (14.3)	2 (14.3)	3 (21.4)

Period 1 was from Day 1 panobinostat date (inclusive) to first ketoconazole dose date exclusive).

Period 2 was from first ketoconazole dose (inclusive) to ketoconazole and panobinostat combo date (exclusive); Period 3 was from ketoconazole and panobinostat combo date (inclusive) to first extension panobinostat dose date (exclusive).

Primary SOCs were presented alphabetically; Preferred terms were sorted within primary SOC by descending order of frequencies, as reported in the last column.

A patient with multiple occurrences of an AE in 1 period was counted only once in the AE category for that period.

A patient with multiple AEs within a primary SOC was counted only once in the total row.

If an AE occurred after taking study drug in Period x and prior to taking the study drug in Period x+1 (or up to the end of study), this AE was accounted for under the treatment given in Period x.

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and period (preferred term occurring in at least 10% of the patients) - Extension phase (Safety set patients who entered the extension phase)

Primary System Organ Class **Preferred Term**	**All Patients** **N=13** **n (%)**
-**Any primary system organ class**	
- Total	13 (100)
Blood and lymphatic system disorders	
-Total	4 (30.8)
Thrombocytopenia	4 (30.8)
Neutropenia	2 (15.4)
Cardiac disorders	
-Total	2 (15.4)
Myocardial infarction	2 (15.4)
Gastrointestinal disorders	
-Total	11 (84.6)
Nausea	9 (69.2)
Diarrhoea	8 (61.5)
Vomiting	8 (61.5)
Abdominal discomfort	2 (15.4)
Abdominal pain	2 (15.4)
Constipation	2 (15.4)
General disorders and administration site conditions	
-Total	9 (69.2)
Fatigue	7 (53.8)
Oedema peripheral	4 (30.8)
Performance status decreased	3 (23.1)
Chills	2 (15.4)
Pyrexia	2 (15.4)
Infections and infestations	
-Total	4 (30.8)
Nasopharyngitis	2 (15.4)
Metabolism and nutrition disorders	
-Total	11 (84.6)
Anorexia	7 (53.8)
Hypophosphataemia	6 (46.2)
Dehydration	4 (30.8)
Hypokalaemia	4 (30.8)
Hyponatraemia	3 (23.1)

Hypocalcaemia	2 (15.4)
Musculoskeletal and connective tissue disorders	
-Total	9 (69.2)
Myalgia	3 (23.1)
Arthralgia	2 (15.4)
Pain in extremity	2 (15.4)
Nervous system disorders	
-Total	4 (30.8)
Dizziness	2 (15.4)
Respiratory, thoracic and mediastinal disorders	
-Total	8 (61.5)
Dyspnoea	3 (23.1)
Cough	2 (15.4)
Dysphonia	2 (15.4)
Oropharyngeal pain	2 (15.4)

Note: - Primary system organ classes are presented alphabetically; Preferred terms were sorted within primary

SOC by descending order of frequencies.

A patient with multiple occurrences of an AE was counted only once in the AE category.

A patient with multiple AEs within a primary SOC was counted only once in the total row.

Adverse events, suspected to be study drug related, by primary system organ class, preferred term, and period (preferred term occurring in at least 10% of the patients) – core phase (Safety set)

Primary System Organ Class Preferred Term	Period 1 N=14 n (%)	Period 2 N=14 n (%)	Period 3 N=14 n (%)	All Patients N=14 n (%)
-**Any primary system organ class**				
-Total	8 (57.1)	5 (35.7)	7 (50.0)	12 (85.7)
Gastrointestinal disorders				
-Total	7 (50.0)	1 (7.1)	4 (28.6)	9 (64.3)
Diarrhoea	2 (14.3)	0 (0.0)	3 (21.4)	4 (28.6)
Vomiting	4 (28.6)	0 (0.0)	0 (0.0)	4 (28.6)
Nausea	2 (14.3)	1 (7.1)	2 (14.3)	3 (21.4)
General disorders and administration				
site conditions				
-Total	2 (14.3)	1 (7.1)	1 (7.1)	3 (21.4)
Fatigue	2 (14.3)	0 (0.0)	1 (7.1)	2 (14.3)
Metabolism and nutrition disorders				
-Total	2 (14.3)	2 (14.3)	1 (7.1)	4 (28.6)
Anorexia	2 (14.3)	2 (14.3)	0 (0.0)	4 (28.6)
Musculoskeletal and connective tissue disorders				
-Total	0 (0.0)	0 (0.0)	2 (14.3)	2 (14.3)
Myalgia	0 (0.0)	0 (0.0)	2 (14.3)	2 (14.3)

Primary SOCs were presented alphabetically; Preferred terms were sorted within primary SOC by descendingorder of frequencies, as reported in the last column.

A patient with multiple occurrences of an AE in one period was counted only once in the AE category for thatperiod.

A patient with multiple AEs within a primary SOC was counted only once in the total row.

Period 1 was from Day 1 panobinostat date (inclusive) to first ketoconazole dose date exclusive); Period 2 wasfrom first ketoconazole dose (inclusive) to ketoconazole and panobinostat combo date (exclusive); Period 3 wasfrom ketoconazole and panobinostat combo date (inclusive) to first extension panobinostat dose date (exclusive).

If an AE occurred after taking study drug in period x and prior to taking the study drug in period x+1 (or up to theEOS), this AE was accounted for under the treatment given in period x.

Adverse events, suspected to be study drug related, by primary system organ class, preferred term, and period (preferred term occurring in at least 10% of the patients) – Extension phase (Safety set patients who entered the extension phase)

Primary System Organ Class Preferred Term	All Patients N=13 n (%)
Any primary system organ class	
-Total	13 (100)
Blood and lymphatic system disorders	
-Total	4 (30.8)
Thrombocytopenia	4 (30.8)
Neutropenia	2 (15.4)
Gastrointestinal disorders	
-Total	8 (61.5)
Nausea	7 (53.8)
Vomiting	6 (46.2)
Diarrhoea	5 (38.5)
General disorders and administration site conditions	
-Total	8 (61.5)
Fatigue	7 (53.8)
Performance status decreased	2 (15.4)
Metabolism and nutrition disorders	
-Total	8 (61.5)
Anorexia	5 (38.5)
Hypophosphataemia	4 (30.8)
Primary SOCs were presented alphabetically; Preferred terms were sorted within primary SOC by descendingorder of frequencies. A patient with multiple occurrences of an AE was counted only once in the AE category. A patient with multiple AEs within a primary SOC was counted only once in the total row.	

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

	Panobinostat
Nausea	9 (69.2)
Diarrhoea	8 (61.5)
Vomiting	8 (61.5)
Fatigue	7 (53.8)
Anorexia	7 (53.8)
Hypophosphataemia	6 (46.2)
Thrombocytopenia	4 (30.8)
Oedema peripheral	4 (30.8)
Dehydration	4 (30.8)
Hypokalaemia	4 (30.8)

Serious Adverse Events and Deaths

Core Phase

	Panobinostat
No. (%) of subjects studied	14
No. (%) of subjects with AE(s)	14 (100)
Number (%) of subjects with serious or other significant events	2 (14.3)
Death	0 (0)
SAE(s)	2 (14.3)*
Discontinued due to SAE(s)	1 (7.1)
SAEs: 1 renal failure, 1 dyspnea and hypoxia	

Extension Phase

	Panobinostat
No. (%) of subjects studied	13
No. (%) of subjects with AE(s)	13 (100)
Number (%) of subjects with serious or other significant events	7 (53.8)
Death[1]	1 (7.7)
SAE(s)	7 (53.8)
Discontinued due to SAE(s)	1 (23.1)
[1]One death occurred during the Extension Phase due to myocardial infarction 6 days after the patient had received the last dose of study medication.	

Date of Clinical Trial Report 17 Mar 2011 (CSR final but not published)
Date Inclusion on Novartis Clinical Trial Results Database 11 Apr 2011
Date of Latest Update