Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Advanced solid tumors, clinical pharmacology

Approved Indication

Investigational

Study Number

CLBH589B2109

Title

A phase IB, open-label, multicenter study to investigate the effect of oral panobinostat on dextromethorphan, a CYP2D6 substrate, and to assess the efficacy and safety of oral panobinostat in patients with advanced solid tumors

Phase of Development

Phase Ib

Study Start/End Dates

15-Nov-2007/22-Jan-2009

Study Design/Methodology

Open-label, multiple dose, single sequence crossover study. The study design included two phases: core (10 days) and extension. During the core phase oral panobinostat was administered once per day, on Days 3, 5, and 8 and oral DM on the mornings of Day 1 and Day 8. In the extension phase only oral panobinostat was administered, three times a week until disease progression or intolerability of the study drug.

Centres

5 centers in 2 countries: Canada (1), USA (4)

Publication

None

Objectives

Primary objective(s)

- determine the effect of oral panobinostat on the pharmacokinetics (PK) of dextromethorphan (DM) and its metabolite, dextrorphan (DX), in patients who are extensive metabolizers (EMs) (core study).

Secondary objective(s)

- determine the effect of oral panobinostat on the PK of DM and its CYP3A-mediated metabolites, e.g. 3-methoxymorphinan (MEM), core phase
- assess the safety and tolerability of oral panobinostat when co-administered with DM (core phase)
- assess the efficacy of oral panobinostat monotherapy (extension phase)
- assess safety and tolerability of oral panobinostat monotherapy.

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

Oral panobinostat as a 5 mg or 20 mg hard gelatin capsule.

Dextromethorphan hydrobromide 15 mg liquid-filled capsules (Robitussin DM cough gel) for oral administration.

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

Not applicable

Criteria for Evaluation

Primary variables (Pharmacology)

PK samples were drawn at specific times during the first 10 days of the study. Dextromethorphan (DM) and total (=free+glucuronidated) Dextrorphan (DX) plasma concentrations were measured, using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Secondary variables

The remainder of the banked plasma samples for DM/DX analysis were analyzed for 3-Methoxymorphinan (3-MEM) using a validated method.

Tumor response was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) during the extension phase.

Safety and tolerability

Adverse events (AEs), standard laboratory parameters, vital signs, ECGs

Other: Pharmacogenetic

CYP2D6 genotyping was performed using baseline DNA samples from consenting patients. Genotypes were then classified according to the established literature into extensive metabolizers (EM), poor metabolizers (PM), intermediate metabolizers (IM) or ultra extensive metabolizers (UM). IM, EM and UM were considered as CYP2D6 EM. However, when CYP2D6 genotype was not obtained or determined, the parent/metabolite ratio (MR) of DM/DX in plasma was used for the classification of patients. Patients with an MR DM/DX = 0.3 were considered PMs, whereas those with an MR (DM/DX) < 0.3 were considered EMs.

Statistical Methods

The primary focus of the statistical hypothesis was to demonstrate a lack of drug-drug interaction (DDI) in DM PK parameters in EM patients only. Lack of DDI was concluded when the 90% confidence interval for the ratio of DM + panobinostat to DM alone was completely contained within the range 0.80 to 1.25 for AUC and C_{max} of DM. A minimum of 12 patients who were EMs, and completing the core study, were required to meet the primary endpoint. A formal statistical analysis was performed for AUC_{0-24}, AUC_{0-48}, AUC_{0-inf}, C_{max}, and MR of DM/DX. A linear mixed effects model was fitted to the log-transformed PK parameters. Included in the model was treatment (DM + panobinostat or reference (DM alone)) as fixed effects, and patient as a random effect. Proper contrasts were used to estimate the treatment differences (i.e., DM + panobinostat vs. DM alone). The point estimate of the treatment difference and the corresponding 90% 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. T_{max} was analyzed using non-parametric method.

The assessment of safety was based mainly on the frequency and severity of adverse events and

the frequency of laboratory values (hematology, 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

The study population included adult patients, aged 18 years and older, who had histologically or cytologically confirmed advanced or metastatic incurable solid tumor as documented by computed tomography (CT) or magnetic resonance imaging (MRI) that had already progressed on standard therapies or who were following standard therapies and agreed to stop the therapies in order to enroll in this study

Number of Subjects

Disposition	All patients (N=17)
	n (%)
End of treatment	
Primary reason for end of treatment	
Adverse event(s)	4 (23.5)
Abnormal laboratory value(s)	1 (5.9)
Patient withdrew consent	1 (5.9)
Disease progression	11 (64.7)

Analysis Sets

Analysis set	All patients (N=17)
	n (%)
Core phase:	
PK - DM	14 (82.4)
PK - DX	14 (82.4)
PK -3-MEM	10 (58.8)
Safety	17 (100.0)
Extension phase:	
Safety (patients who entered the extension)	16 (94.1)
Efficacy	16 (94.1)

Demographic and Background Characteristics

Demographic variable		All patients (N = 17)
Age (years)	n	17
	Mean (SD)	64.6 (7.04)
Sex - n (%)	Male	10 (58.8)
	Female	7 (41.2)
Race - n (%)	Caucasian	11 (64.7)
	Black	4 (23.5)
	Asian	2 (11.8)
Ethnicity - n (%)	Japanese	2 (11.8)
	Other	15 (88.2)
Baseline ECOG performance status	0	5 (29.4)
	1	9 (52.9)
	2	3 (17.6)
CY2D6 phenotype	Extensive metabolizer (EM) from biomarker	9 (52.9)
	Extensive metabolizer from metabolic ratio	2 (11.8)
	Intermediate metabolizer (IM) from genotyping	4 (23.5)
	No genotyping or metabolic ratio data	1 (5.9)

	Genotyping result “Not determined”	1 (5.9)	

Primary Objective Results

Geometric mean ratio (90% CI) of dextromethorphan (DM) primary PK parameters in extensive metabolizers (PK set - DM)

DM PK parameter (unit)	Treatment	n 1	Adjusted geo-mean	Comparison(s)	Treatment comparison 90% CI Geo-mean ratio	Lower	Upper
C_{max}	Ref	14	5.114				
(ng/mL)	Test	14	9.376	Test:Ref	1.83	1.438	2.338
AUC_{0-48}	Ref	14	61.371				
(ng.h/mL)	Test	14	85.891	Test:Ref	1.52	1.128	2.059
AUC_{0-inf}	Ref	12	55.076				
(ng.h/mL)	Test	13	90.527	Test:Ref	1.64	1.169	2.312
T_{max} (h)	Ref	14	2.500				
	Test	14	1.835	Test - Ref	-0.48	-1.680	1.500
MR	Ref	13	0.011				
	Test	14	0.013	Test:Ref	1.21	0.922	1.595

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

[1] n = number of patients with non-missing values.

Geo-mean = geometric mean. Geo-mean, Geo-mean ratio, and 90% CI were all determined from a mixed effect model and back-transformed from log scale.

The model on log transformed PK parameters includes treatment (panobinostat + dextromethorphan or dextromethorphan alone) as fixed effect, and patient as a random effect.

For T_{max}, median was presented under “Geo-Mean”, median of difference (Test - Reference) under “Geo-mean ratio”, minimum and maximum difference under “Lower” and “Upper”.

Extensive metabolizers include: ultra extensive, extensive and intermediate metabolizers.

Secondary Objective Results

Summary of statistical analysis of plasma 3-methoxymorphinan (3-MEM) primary PK parameters (PK set - 3-MEM)

3-MEM PK parameter (unit)	Treatment	n 1	Adjusted geo-mean	Comparison(s)	Treatment comparison 90% CI Geo-mean ratio	Lower	Upper
C_{max}	Ref	10	0.519				
(ng/mL)	Test	10	0.529	Test:Ref	1.02	0.852	1.222
$AUC_{(0-24)}$	Ref	4	14.559				
(ng.h/mL)	Test	4	13.973	Test:Ref	0.96	0.738	1.248
T_{max}(h)	Ref	10	1.750				
	Test	10	3.000	Test - Ref	1.00	-1.500	19.000

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

n [1]= number of patients with non-missing values.

Geo-mean = geometric mean. Geo-mean, Geo-mean ratio, and 90% CI were all determined from a mixed effect model and back-transformed from log scale. The model on log transformed PK parameters includes treatment (panobinostat + dextromethorphan or dextromethorphan alone) as fixed effect, and patient as a random effect. For T_{max}, median was presented under “Geo-Mean”, median of difference (Test - Reference) under “Geo-mean ratio”, minimum and maximum difference under “Lower” and “Upper”.

Best overall response (Efficacy set)

Best overall response	**Panobinostat**
	N=16
	n (%)
Complete response (CR)	0 (0.0)
Partial response (PR)	1 (6.3)
Stable disease (SD)	3 (18.8)
Progressive disease	6 (37.5)
Unknown	6 (37.5)
CR/PR	1 (6.3)
95% CI	(0.16, 30.23)
CR/PR/SD	4 (25.0)
95% CI	(7.27, 52.38)

Safety Results

Adverse events, regardless of study treatment relationship, by primary system organ class (SOC) - core phase (Safety set)

System organ class	Number (%) patients N=17
Any primary SOC - Total	15 (88.2)
Blood and lymphatic system disorders	1 (5.9)
Gastrointestinal disorders	12 (70.6)
General disorders and administration site conditions	5 (29.4)
Infections and infestations	1 (5.9)
Investigations	1 (5.9)
Metabolism and nutrition disorders	4 (23.5)
Musculoskeletal and connective tissue disorders	2 (11.8)
Nervous system disorders	2 (11.8)
Psychiatric disorders	1 (5.9)
Respiratory, thoracic and mediastinal disorders	2 (11.8)

Adverse events, regardless of study treatment relationship, by preferred term (occurring in at least 10% of the patients) - core phase (Safety set)

Preferred term	Number (%) patients (N=17)
Total	15 (88.2)
Nausea	6 (35.3)
Diarrhoea	4 (23.5)
Constipation	3 (17.6)
Fatigue	3 (17.6)
Gastrooesophageal reflux disease	2 (11.8)
Hypomagnesaemia	2 (11.8)
Myalgia	2 (11.8)

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

System Organ Class	n (%) patients (N=16)
Any primary SOC - Total	16 (100.0)
Blood and lymphatic system disorders	6 (37.5)
Cardiac disorders	2 (12.5)
Endocrine disorders	1 (6.3)

Gastrointestinal disorders	8 (50.0)	
General disorders and administration site conditions	9 (56.3)	
Infections and infestations	7 (43.8)	
Injury, poisoning and procedural complications	1 (6.3)	
Investigations	5 (31.3)	
Metabolism and nutrition disorders	5 (31.3)	
Musculoskeletal and connective tissue disorders	3 (18.8)	
Nervous system disorders	2 (12.5)	
Psychiatric disorders	5 (31.3)	
Renal and urinary disorders	2 (12.5)	
Respiratory, thoracic and mediastinal disorders	9 (56.3)	
Skin and subcutaneous tissue disorders	1 (6.3)	
Vascular disorders	2 (12.5)	

Adverse events, regardless of study drug relationship, by preferred term (occurring in at least 10% of patients) - extension phase (Safety set)

Preferred term	Number (%) patients (N= 16)
Total	16 (100.0)
Dyspnoea	7 (43.8)
Fatigue	6 (37.5)
Oedema peripheral	4 (25.0)
Thrombocytopenia	4 (25.0)
Urinary tract infection	4 (25.0)
Cough	3 (18.8)
Non-cardiac chest pain	3 (18.8)
Pneumonia	3 (18.8)
Abdominal distension	2 (12.5)
Anaemia	2 (12.5)
Anorexia	2 (12.5)
Back pain	2 (12.5)
Confusional state	2 (12.5)
Dehydration	2 (12.5)
Dyspepsia	2 (12.5)
Hypokalemia	2 (12.5)
Hypotension	2 (12.5)
Pain in extremity	2 (12.5)
Vomiting	2 (12.5)
Weight decreased	2 (12.5)

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events – extension phase (Safety set)

Serious or significant event	All patients (N=16) n (%)
On treatment deaths including deaths within 28 days after last dose of study drug	3 (18.8)
All SAEs	7 (43.8)
Clinically significant AEs	1 (6.3)

The SAEs were 3 incidents of pneumonia (2 patients, one also reporting one incident of sepsis); 2 incidents of intermittent claudication, pain in extremity, peripheral ischemia (all in 1 patient); fever, acute renal failure and hypokalemia (1 patient); urinary tract infection (1 patient); atrial fibrillation and cerebral hemorrhage (1 patient; these events were also deemed clinically significant); respiratory distress (1 patient)

Other Relevant Findings

None

Date of Clinical Trial Report 17-Nov-2009
Date Inclusion on Novartis Clinical Trial Results Database 20-Jan-2010
Date of Latest Update