



## Clinical trial results:

### A Phase II Study of Oral Panobinostat in Adult Patients with Relapsed/Refractory Classical Hodgkins lymphoma after High-dose Chemotherapy with Autologous Stem Cell Transplant

#### Summary

EudraCT number	2008-003016-35
Trial protocol	ES DE FR BE GB IT
Global end of trial date	12 August 2013

#### Results information

Result version number	v2 (current)
This version publication date	12 August 2021
First version publication date	29 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Additional data being added to Outcomes along with correction to participant flow.

#### Trial information

##### Trial identification

Sponsor protocol code	CLBH589E2214
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00742027
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002 , Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of oral panobinostat in patients with refractory/relapsed classical HL who have received prior treatment with high dose chemotherapy and autologous stem cell transplant. Safety of panobinostat will also be assessed. Other markers that may correlate with efficacy or safety will be explored.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	129
EEA total number of subjects	54

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	123
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 102 participants were to be enrolled and treated in the study. However, 129 participants got enrolled and analyzed, out of which no participant completed the study.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Panobinostat
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Arm description:

Participants received panobinostat 40 mg, capsules, orally, thrice every week (i.e. days 1, 3 and 5), in each cycle of 21 days until unacceptable toxicity, disease progression, start of new anti-cancer therapy or withdrawal of consent (up to approximately 48 months).

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral panobinostat was supplied as 5 mg or 20 mg hard gelatin capsules and was given on a flat scale of mg on a given day.

Number of subjects in period 1	Panobinostat
Started	129
Completed	0
Not completed	129
Consent withdrawn by subject	18
Disease progression	76
Death	7
Administrative Problems	1
New Cancer Therapy	19
Follow up Phase Completed As Per Protocol	2
Lost to follow-up	4
Missing	2



## Baseline characteristics

### Reporting groups

Reporting group title	Panobinostat
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Reporting group description:

Participants received panobinostat 40 mg, capsules, orally, thrice every week (i.e. days 1, 3 and 5), in each cycle of 21 days until unacceptable toxicity, disease progression, start of new anti-cancer therapy or withdrawal of consent (up to approximately 48 months).

Reporting group values	Panobinostat	Total	
Number of subjects	129	129	
Age categorical Units: Subjects			
< 65	123	123	
≥ 65	6	6	
Age continuous Units: years arithmetic mean standard deviation	34.7 ± 12.24	-	
Gender categorical Units: Subjects			
Female	63	63	
Male	66	66	

## End points

### End points reporting groups

Reporting group title	Panobinostat
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Reporting group description:

Participants received panobinostat 40 mg, capsules, orally, thrice every week (i.e. days 1, 3 and 5), in each cycle of 21 days until unacceptable toxicity, disease progression, start of new anti-cancer therapy or withdrawal of consent (up to approximately 48 months).

### Primary: Objective response rate to therapy with oral panobinostat in patients with refractory/relapsed classical Hodgkin Lymphoma (HL)

End point title	Objective response rate to therapy with oral panobinostat in patients with refractory/relapsed classical Hodgkin Lymphoma (HL) <sup>[1]</sup>
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End point description:

Objective Response defined by RECIST criteria: Partial response (PR) must have  $\geq 30\%$  decrease in the sum of the longest diameter of all target lesions, from the baseline sum. Complete response (CR) must have disappearance of all target and non-target lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments within 4 weeks. Progression = 20% increase in the sum of the longest diameter of all target lesions, from the smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or progression of non-target lesions. This is a single arm study and as such there were no comparison statistics performed.

End point type	Primary
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End point timeframe:

32 weeks from start of treatment; cut-off date 11-Jun-2010

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses have been reported for this primary end point.

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: Percentage of participants				
number (not applicable)				
Complete response	3.9			
Partial response	23.3			
Stable disease	55			
Progressive disease	10.9			
Unknown	7			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Response rate based on central review of CT scan/MRI

End point title	Response rate based on central review of CT scan/MRI
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End point description:

Best overall disease response recorded from the start of treatment until progression/recurrence or the

start of new cancer therapy.

End point type	Secondary
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End point timeframe:

From start of treatment until progression/recurrence or start of a new cancer therapy up to Data cut-off 11Jun2010

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: Percentage of participants				
number (not applicable)				
Complete response	0.8			
Partial response	20.9			
Stable disease	56.6			
Progressive disease	15.5			
Unknown	6.2			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to overall disease response in responders

End point title	Time to overall disease response in responders
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End point description:

Time to overall disease response (CR or PR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease response (PR or CR).

End point type	Secondary
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End point timeframe:

From start of treatment up to Data cut-off 11Jun2010

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	35 <sup>[2]</sup>			
Units: weeks				
median (confidence interval 95%)	9.9 (6 to 12.1)			

Notes:

[2] - Number of responders

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of overall disease response

End point title	Duration of overall disease response
End point description: Duration of overall response (CR or PR) is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.	
End point type	Secondary
End point timeframe: From start of treatment up to Data cut-off 11Jun2010	

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	35 <sup>[3]</sup>			
Units: weeks				
median (confidence interval 95%)	30.1 (17.4 to 35.9)			

Notes:

[3] - Number of responders

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description: Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.	
End point type	Secondary
End point timeframe: From start of treatment up to database lock 14Feb2014	

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: months				
median (confidence interval 95%)	6.1 (5.4 to 8.3)			

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival

End point title	Overall survival
End point description:	Overall survival (OS) is the duration from date of randomization to date of death from any cause
End point type	Secondary
End point timeframe:	Baseline to date of death from any cause; with a cut-off / DBL of 14-Feb-2014

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: months				
median (full range (min-max))	34.9 (0.7 to 53)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Concentration (Cmax) of Panobinostat

End point title	Maximum Observed Concentration (Cmax) of Panobinostat
End point description:	
End point type	Secondary
End point timeframe:	Cycle 1, Day 1: Pre-dose, 0.25, 1, 3, 5, 7, 24, and 28 hours post-dose

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[4]</sup>			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	41.88 (± 22.165)			

Notes:

[4] - Pharmacokinetic set (PK) included all participants who have received at least one dose of panobinostat

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Time to Reach Maximum Plasma Concentration (Tmax) of Panobinostat

End point title	The Time to Reach Maximum Plasma Concentration (Tmax) of
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End point description:

End point type Secondary

End point timeframe:

Cycle 1, Day 1: Pre-dose, 0.25, 1, 3, 5, 7, 24, and 28 hours post-dose

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[5]</sup>			
Units: hours				
median (full range (min-max))	1.1 (0.30 to 6.10)			

Notes:

[5] - PK population included all participants who have received at least one dose of panobinostat.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to 28 Hours (AUC<sub>0-28</sub>) for Panobinostat**End point title Area Under the Plasma Concentration-Time Curve From Time Zero to 28 Hours (AUC<sub>0-28</sub>) for Panobinostat

End point description:

End point type Secondary

End point timeframe:

Cycle 1, Day 1: Pre-dose, 0.25, 1, 3, 5, 7, 24, and 28 hours post-dose

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	13 <sup>[6]</sup>			
Units: hour*nanograms per milliliter (h.ng/ mL)				
arithmetic mean (standard deviation)	233.38 (± 112.138)			

Notes:

[6] - PK population included all participants who have received at least one dose of panobinostat.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUC<sub>0-∞</sub>) for Panobinostat**

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUC <sub>0-∞</sub> ) for Panobinostat
End point description:	
End point type	Secondary
End point timeframe:	
Cycle 1, Day 1: Pre-dose, 0.25, 1, 3, 5, 7, 24, and 28 hours post-dose	

<b>End point values</b>	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	11 <sup>[7]</sup>			
Units: h.ng/mL				
arithmetic mean (standard deviation)	239.36 (± 104.263)			

Notes:

[7] - PK population included all participants who have received at least one dose of panobinostat.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

### Reporting groups

Reporting group title	Panobinostat 40mg, 3 x week, q week
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Reporting group description:

Panobinostat 40mg, 3 x week, q week

<b>Serious adverse events</b>	Panobinostat 40mg, 3 x week, q week		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 129 (39.53%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cervicitis human papilloma virus			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
<b>Confusional state</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Depression</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Mental status changes</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Atrial fibrillation</b>			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
<b>Pericardial effusion</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Sinus tachycardia</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Ventricular hypokinesia</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			

Dizziness				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial venous sinus thrombosis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nerve root compression				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral nerve lesion				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
subjects affected / exposed	5 / 129 (3.88%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
<b>Febrile neutropenia</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Haemorrhagic disorder</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Idiopathic thrombocytopenic purpura</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Neutropenia</b>			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Thrombocytopenia</b>			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences causally related to treatment / all	12 / 12		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
<b>Abdominal pain</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Colitis</b>			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Diarrhoea</b>			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Gastritis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nausea</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Upper gastrointestinal haemorrhage</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Vomiting</b>			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders</b>			
<b>Cholecystitis acute</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cholelithiasis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			

Renal failure acute			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urethral haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Appendicitis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Bronchopneumonia</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cellulitis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Dengue fever</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Device related infection</b>			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Device related sepsis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infection</b>			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Necrotising ulcerative gingivostomatitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 129 (3.88%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
<b>Septic shock</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Sinusitis</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Metabolism and nutrition disorders</b>			
<b>Cachexia</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Dehydration</b>			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Decreased appetite</b>			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Panobinostat 40mg, 3 x week, q week		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 129 (100.00%)		
<b>General disorders and administration site conditions</b>			
<b>Chills</b>			

subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Asthenia			
subjects affected / exposed	24 / 129 (18.60%)		
occurrences (all)	33		
Fatigue			
subjects affected / exposed	60 / 129 (46.51%)		
occurrences (all)	93		
Non-cardiac chest pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	17 / 129 (13.18%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	56 / 129 (43.41%)		
occurrences (all)	95		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 129 (27.91%)		
occurrences (all)	46		
Dyspnoea			
subjects affected / exposed	23 / 129 (17.83%)		
occurrences (all)	26		
Epistaxis			
subjects affected / exposed	15 / 129 (11.63%)		
occurrences (all)	30		
Oropharyngeal pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	11		
Wheezing			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	8		
Productive cough			

subjects affected / exposed occurrences (all)	10 / 129 (7.75%) 13		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	12		
Depression			
subjects affected / exposed	11 / 129 (8.53%)		
occurrences (all)	11		
Anxiety			
subjects affected / exposed	16 / 129 (12.40%)		
occurrences (all)	18		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	11		
Weight decreased			
subjects affected / exposed	16 / 129 (12.40%)		
occurrences (all)	19		
Blood creatinine increased			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	26		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	8		
Tachycardia			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			

subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 10		
Dysgeusia subjects affected / exposed occurrences (all)	21 / 129 (16.28%) 29		
Headache subjects affected / exposed occurrences (all)	27 / 129 (20.93%) 42		
Lethargy subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 13		
<b>Blood and lymphatic system disorders</b>			
Neutropenia subjects affected / exposed occurrences (all)	36 / 129 (27.91%) 113		
Anaemia subjects affected / exposed occurrences (all)	52 / 129 (40.31%) 120		
Leukopenia subjects affected / exposed occurrences (all)	16 / 129 (12.40%) 29		
Thrombocytopenia subjects affected / exposed occurrences (all)	109 / 129 (84.50%) 360		
<b>Gastrointestinal disorders</b>			
Constipation subjects affected / exposed occurrences (all)	25 / 129 (19.38%) 33		
Abdominal pain upper subjects affected / exposed occurrences (all)	21 / 129 (16.28%) 26		
Abdominal pain subjects affected / exposed occurrences (all)	17 / 129 (13.18%) 32		
Diarrhoea			

subjects affected / exposed occurrences (all)	96 / 129 (74.42%) 219		
Dry mouth subjects affected / exposed occurrences (all)	14 / 129 (10.85%) 17		
Dyspepsia subjects affected / exposed occurrences (all)	12 / 129 (9.30%) 18		
Stomatitis subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 12		
Nausea subjects affected / exposed occurrences (all)	87 / 129 (67.44%) 158		
Vomiting subjects affected / exposed occurrences (all)	55 / 129 (42.64%) 103		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 8		
Petechiae subjects affected / exposed occurrences (all)	12 / 129 (9.30%) 13		
Dry skin subjects affected / exposed occurrences (all)	13 / 129 (10.08%) 18		
Pruritus subjects affected / exposed occurrences (all)	21 / 129 (16.28%) 26		
Rash subjects affected / exposed occurrences (all)	11 / 129 (8.53%) 11		
Endocrine disorders Hypothyroidism			

subjects affected / exposed occurrences (all)	20 / 129 (15.50%) 22		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	14		
Back pain			
subjects affected / exposed	24 / 129 (18.60%)		
occurrences (all)	35		
Muscle spasms			
subjects affected / exposed	30 / 129 (23.26%)		
occurrences (all)	39		
Bone pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	14 / 129 (10.85%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Musculoskeletal chest pain			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	13		
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	10		
Nasopharyngitis			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	17		
Lower respiratory tract infection			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	9		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	19 / 129 (14.73%) 27		
Sinusitis subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 20		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 12		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	48 / 129 (37.21%) 61		
Dehydration subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 8		
Hypokalaemia subjects affected / exposed occurrences (all)	19 / 129 (14.73%) 49		
Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 9		
Hypophosphataemia subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 46		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2009	<ul style="list-style-type: none"><li>• Removal of requirement for patients to have prior exposure to gemcitabine, vinblastine, or vinorelbine.</li><li>• Dosing with panobinostat without regard to food was permitted.</li><li>• Clarification was provided regarding response assessment in the study, stating that a 4 week post response confirmatory scan was not required.</li><li>• Clarified that there would be no enrollment hold between stage 1 to 2, in light of additional safety and efficacy data.</li><li>• All references to the Data Monitoring Committee were changed to Steering Committee to accurately identify the name of the committee and their role in the study since some of the committee members are clinical investigators on the study.</li></ul>
04 August 2009	<ul style="list-style-type: none"><li>• Provided additional guidance on dose modifications: For patients who do not tolerate every week (qw) dosing, dose modification will allow changing the drug administration schedule to an every other week (qow) dosing in addition to decreasing the dose. For patients who have been tolerating reduced doses, dose re-escalation may also be allowable to seek maximal clinical benefit from panobinostat.</li><li>• Starting dose remained unchanged at 40 mg 3xweek, every week to allow for maximum dose intensity upfront to combat tumor burden.</li><li>• For those patients who become intolerant to this every week dosing schedule, changing to an every other week dosing schedule was permitted. Preliminary data from and ongoing Study E2214 showed that the every other week schedule may be better tolerated and was anticipated to help patients sustain continued exposure and therefore potentially achieve maximal benefit from panobinostat. Dose intensity below 30 mg, 3 x week, every week or 20 mg, 3 x week, every week were not permitted as the plasma concentrations at lower dose intensity may not have maintained the histone acetylation for prolonged period of time and thus could possibly be subtherapeutic.</li></ul>
22 August 2011	<ul style="list-style-type: none"><li>• Provided instructions on continuation of treatment and on necessary safety investigations for ongoing patients.</li><li>• No further efficacy data captured other than documentation of the date of disease progression as assessed by investigator and death on study, as applicable. Laboratory and other safety assessments reduced to that which is appropriate to adequately monitor and protect patient safety. Patients had their data further summarized and/or listed as applicable in a subsequent extension report once these patients had either completed or discontinued the study.</li><li>• Section added to provide updated data from Study E2214 interim analysis</li><li>• Updated the study design, assessments and central review</li><li>• Indicated completeness of enrollment as of 30-Oct-2009 in section on population</li><li>• Clarified requirements for ECG monitoring</li><li>• Updates on study duration and follow up requirements</li><li>• Updates to reflect current program guidance for co-administration of CYP2D6 substrates</li><li>• Updates to reflect current program guidance for co-administration of CYP3A4/5 inducers and inhibitors</li><li>• Updated the pregnancy guidance for panobinostat</li><li>• Updated the section on supportive analyses</li></ul>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported