# Clinical trial results:
# A Phase II Study of Oral Panobinostat in Adult Patients with Relapsed/Refractory Classical Hodgkins lymphoma after Failure of High-dose Chemotherapy with Autologous Stem Cell Transfusion and a Gemcitabine- or Vinorelbine- or Vinblastine-Containing Treatment Regimen

## 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 | v1 |
| This version publication date | 13 July 2016 |
| First version publication date | 29 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CLBH589E2214 |

**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:

| Subjects enrolled per age group | |
|---|---|
| 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 patients were to be enrolled and treated in the study. 129 patients were enrolled and analyzed.

### 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 |

Arm description:

All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle.

| | |
|---|---|
| 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 | 1 |
| Not completed | 128 |
| Adverse event, serious fatal | 1 |
| Consent withdrawn by subject | 12 |
| Adverse event, non-fatal | 25 |
| Administrative problems | 1 |
| 'New cancer therapy ' | 11 |
| 'Disease progression ' | 76 |
| Lost to follow-up | 1 |
| Protocol deviation | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Panobinostat |
| Reporting group description: | |
| All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle. | |

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

## End points

### End points reporting groups

| Reporting group title | Panobinostat |
|---|---|

Reporting group description:

All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle.

### 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)[1] |
|---|---|

End point description:

Objective Response defined by RECIST criteria: Partial response (PR) must have ≥ 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 |
|---|---|

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 planned statistical analysis was planned for this outcome measure

| 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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[2] | | | |
| 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

| **End point values** | Panobinostat | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35[3] | | | |
| 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

| **End point values** | 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

| **End point values** | 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

## 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 13.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Panobinostat 40mg, 3 x week, q week |

Reporting group description:

Panobinostat 40mg, 3 x week, q week

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

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

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

| | | | | |
|---|---|---|---|---|
| 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 | | | |
| Infections and infestations | | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 1 / 129 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopneumonia | | | | |
| subjects affected / exposed | 1 / 129 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 1 / 129 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dengue fever | | | | |
| subjects affected / exposed | 1 / 129 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 2 / 129 (1.55%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related sepsis | | | | |
| subjects affected / exposed | 1 / 129 (0.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 24 / 129 (18.60%) | | |
| occurrences (all) | 33 | | |
| Chills | | | |
| subjects affected / exposed | 8 / 129 (6.20%) | | |
| occurrences (all) | 8 | | |
| 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 | | |
| Productive cough | | | |
| subjects affected / exposed | 10 / 129 (7.75%) | | |
| occurrences (all) | 13 | | |
| Wheezing | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 129 (5.43%) | | |
| occurrences (all) | 8 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 16 / 129 (12.40%) | | |
| occurrences (all) | 18 | | |
| Depression | | | |
| subjects affected / exposed | 11 / 129 (8.53%) | | |
| occurrences (all) | 11 | | |
| Insomnia | | | |
| subjects affected / exposed | 12 / 129 (9.30%) | | |
| occurrences (all) | 12 | | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 7 / 129 (5.43%) | | |
| occurrences (all) | 11 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 10 / 129 (7.75%) | | |
| occurrences (all) | 26 | | |
| Weight decreased | | | |
| subjects affected / exposed | 16 / 129 (12.40%) | | |
| occurrences (all) | 19 | | |
| 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 | 8 / 129 (6.20%) | | |
| occurrences (all) | 10 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 21 / 129 (16.28%) | | |
| occurrences (all) | 29 | | |
| Headache | | | |
| subjects affected / exposed | 27 / 129 (20.93%) | | |
| occurrences (all) | 42 | | |
| Lethargy | | | |
| subjects affected / exposed | 9 / 129 (6.98%) | | |
| occurrences (all) | 13 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 52 / 129 (40.31%) | | |
| occurrences (all) | 120 | | |
| Leukopenia | | | |
| subjects affected / exposed | 16 / 129 (12.40%) | | |
| occurrences (all) | 29 | | |
| Neutropenia | | | |
| subjects affected / exposed | 36 / 129 (27.91%) | | |
| occurrences (all) | 113 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 109 / 129 (84.50%) | | |
| occurrences (all) | 360 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 17 / 129 (13.18%) | | |
| occurrences (all) | 32 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 21 / 129 (16.28%) | | |
| occurrences (all) | 26 | | |
| Constipation | | | |
| subjects affected / exposed | 25 / 129 (19.38%) | | |
| occurrences (all) | 33 | | |
| Diarrhoea | | | |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 20 / 129 (15.50%) | | |
| occurrences (all) | 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 | | |
| Bone pain | | | |
| subjects affected / exposed | 10 / 129 (7.75%) | | |
| occurrences (all) | 13 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 30 / 129 (23.26%) | | |
| occurrences (all) | 39 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 13 / 129 (10.08%) | | |
| 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 | | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 8 / 129 (6.20%) | | |
| occurrences (all) | 10 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 7 / 129 (5.43%) | | |
| occurrences (all) | 9 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 12 / 129 (9.30%) | | |
| occurrences (all) | 17 | | |
| Sinusitis | | | |

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 March 2009 | • Removal of requirement for patients to have prior exposure to gemcitabine, vinblastine, or vinorelbine.<br>• Dosing with panobinostat without regard to food was permitted.<br>• Clarification was provided regarding response assessment in the study, stating that a 4 week post response confirmatory scan was not required.<br>• Clarified that there would be no enrollment hold between stage 1 to 2, in light of additional safety and efficacy data.<br>• 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. |
| 04 August 2009 | • 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.<br>• Starting dose remained unchanged at 40 mg 3×week, every week to allow for maximum dose intensity upfront to combat tumor burden.<br>• 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. |
| 22 August 2011 | • Provided instructions on continuation of treatment and on necessary safety investigations for ongoing patients.<br>• 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.<br>• Section added to provide updated data from Study E2214 interim analysis<br>• Updated the study design, assessments and central review<br>• Indicated completeness of enrollment as of 30-Oct-2009 in section on population<br>• Clarified requirements for ECG monitoring<br>• Updates on study duration and follow up requirements<br>• Updates to reflect current program guidance for co-administration of CYP2D6 substrates<br>• Updates to reflect current program guidance for co-administration of CYP3A4/5 inducers and inhibitors<br>• Updated the pregnancy guidance for panobinostat<br>• Updated the section on supportive analyses |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported