Clinical trial results:
A phase II, open label multicenter trial of panobinostat (LBH589) monotherapy in women with HER2 negative locally recurrent or metastatic breast cancer

Summary

EudraCT number	2008-003176-21
Trial protocol	FR BE IE GB
Global end of trial date	02 April 2015

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	TRIO 017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00777049
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Translational Research in Oncology
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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	27 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2015
Global end of trial reached?	Yes
Global end of trial date	02 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the effect (objective response rate) of oral panobinostat monotherapy in HER2-negative advanced breast cancer population using RECIST criteria as per investigator assessment.

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

A Steering Committee was constituted to supervise the scientific conduct and integrity of the trial. The final protocol and informed consent were reviewed by properly constituted Ethics Committees,and patients enrolled in this study were carefully monitored during the entire treatment phase and were followed as appropriate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2009
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	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Canada: 10
Worldwide total number of subjects	54
EEA total number of subjects	23

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)	40
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 118 evaluable patients were planned to be registered in the study. However due to very low enrollment worldwide and the Risk/ Benefit ratio observed, enrollment was closed early. A total of 80 patients were registered between February 2009 and June 2010 with 54 of them enrolled in the study: 33 in Arm I and 21 in Arm II.

Pre-assignment

Screening details:

80 patients were screened (54 were registered). Participants had to have an Eastern Cooperative Oncology Group Performance of 0, 1 or 2, confirmed invasive breast cancer (HER2-negative), with locally recurrent or radiological evidence of metastatic disease. Radiological tumor measurements were completed prior to registration.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm I

Arm description:

Hormone receptor positive (estrogen and/or progesterone receptor positive), HER2-negative.

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 supplied as a 5mg or 20mg hard gelatin capsule, packaged in HDPE bottles with plastic child resistant closures.

Panobinostat oral 40mg (3 times a week) given every other week as part of a 28 day cycle.

Arm title	Arm II

Arm description:

Hormone receptor negative (estrogen receptor negative and progesterone negative), HER2-negative.

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 supplied as a 5mg or 20mg hard gelatin capsule, packaged in HDPE bottles with plastic child resistant closures.

Panobinostat oral 40mg (3 times a week) given every other week as part of a 28 day cycle.

Number of subjects in period 1	Arm I	Arm II
Started	33	21
Completed	32	20
Not completed	1	1
Consent withdrawn by subject	1	-
Liver enzymes increased (did not start treatment)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm I
Reporting group description:	
Hormone receptor positive (estrogen and/or progesterone receptor positive), HER2-negative.	
Reporting group title	Arm II
Reporting group description:	
Hormone receptor negative (estrogen receptor negative and progesterone negative), HER2-negative.	

Reporting group values	Arm I	Arm II	Total
Number of subjects	33	21	54
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	18	40
From 65-84 years	11	3	14
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.3	52.8	
standard deviation	± 9.5	± 10.7	-
Gender categorical Units: Subjects			
Female	33	21	54
Male	0	0	0
Menopausal Status Units: Subjects			
Premenopausal	0	5	5
Postmenopausal	33	16	49
Race Units: Subjects			
White	31	20	51
Black or African American	1	0	1
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic nor Latino	31	18	49

Subject analysis sets	
Subject analysis set title	Intent-to-treat Population (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat Population (ITT): All registered minus all "screening failure" patients were analyzed in the treatment population to which they were assigned.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all treated patients who received at least one dose of study drug.

Subject analysis set title	Evaluable Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The evaluable population consisted of all enrolled patients minus all those who after review of exclusion and inclusion criteria were found to be ineligible for the study, as well as those who had not received at least one dose of study drug and those who had not had at least one tumor assessment performed after having started the treatment.

Reporting group values	Intent-to-treat Population (ITT)	Safety Population	Evaluable Population
Number of subjects	54	52	40
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	38	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	57.4	58.1	
standard deviation	± 10.5	± 9.8	±
Gender categorical Units: Subjects			
Female	54	52	
Male	0	0	
Menopausal Status Units: Subjects			
Premenopausal	5	4	
Postmenopausal	49	48	
Race Units: Subjects			
White	51	50	

Black or African American	1	0	
Asian	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
American Indian or Alaska Native	0	0	
Other	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic nor Latino	49	47	

End points

End points reporting groups

Reporting group title	Arm I
Reporting group description:	
Hormone receptor positive (estrogen and/or progesterone receptor positive), HER2-negative.	
Reporting group title	Arm II
Reporting group description:	
Hormone receptor negative (estrogen receptor negative and progesterone negative), HER2-negative.	
Subject analysis set title	Intent-to-treat Population (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-treat Population (ITT): All registered minus all “screening failure” patients were analyzed in the treatment population to which they were assigned.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all treated patients who received at least one dose of study drug.	
Subject analysis set title	Evaluable Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The evaluable population consisted of all enrolled patients minus all those who after review of exclusion and inclusion criteria were found to be ineligible for the study, as well as those who had not received at least one dose of study drug and those who had not had at least one tumor assessment performed after having started the treatment.	

Primary: Objective Response Rate (determined by the investigator)

End point title	Objective Response Rate (determined by the investigator)
End point description:	
Assessment of overall response (OR) was based on the response target lesion, non-target lesion, and on presence of new lesions (RECIST criteria version 1.0 using imaging techniques, as per investigator asessment). The timeframe was defined as follows: • Once 21 evaluable patients are reached in Arm I: If less than 3 responses are observed, the arm would be stopped and treatment would be declared ineffective. If at least 3 responses are observed, enrollment would continue to the second stage. • Once 27 evaluable patients are reached in Arm II: If less than 2 responses are observed, the arm would be stopped and treatment would be declared ineffective. If at least 2 responses are observed, enrollment would continue to the second stage. (Please refer to limitations and caveats regarding discontinuation in Arm II and insufficient number of tumour responses in Arm I).	
End point type	Primary
End point timeframe:	
Once 21 (Arm I) / 27 (Arm II) evaluable patients will be treated.	

End point values	Arm I	Arm II	Intent-to-treat Population (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	21	54	
Units: Number of Patients				
Complete Response	0	1	1	
Partial Response	1	0	1	
Stable Disease / Incomplete Response	13	4	17	
Progressive Disease	14	14	28	
Missing	5	2	7	
OBJECTIVE RESPONSE RATE	1	1	2	
DISEASE CONTROL RATE	1	2	3	

Statistical analyses

Statistical analysis title	TRIO-017 Statistical Analysis

Statistical analysis description:

TRIO-017 was designed as a two-stage optimal phase II trial with the following assumptions:
•ineffectiveness cut-off is chosen equal to 4% and effectiveness cut-off equal to 16%. Hence the hypotheses of interest are H0: r ≤ 4% against HA: r ≥ 16% (where r is the response rate)
•type I error rate (α, probability of accepting ineffective treatment, a false positive outcome) is set to 5%
•type II error rate (β, probability of rejecting effective treatment, a false negative outcome) is set to 10%

Comparison groups	Arm I v Arm II
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	other[1]
Parameter estimate	Response Rate
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	14.5

Notes:

[1] - The purpose of the trial is to reject the treatment from further study if it were truly ineffective, and to accept it for further study if it were truly effective within the patient population studied (Arm I and Arm II). The analysis does not compare Arm I against Arm II (both are separate patient populations), and, as such, the hypotheses are separated between the two groups. The response rate is calculated for each treatment group (Arm I and Arm II) separately.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 years and 2 months (time between the first patient registered on 9 February 2009 to the last patient/last visit on 2 April 2015).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Arm I

Reporting group description:

Hormone receptor positive (estrogen and/or progesterone receptor positive), HER2-negative.

Reporting group title	Arm II

Reporting group description:

Hormone receptor negative (estrogen receptor negative and progesterone negative), HER2-negative.

Serious adverse events	Arm I	Arm II	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 32 (37.50%)	8 / 20 (40.00%)	
number of deaths (all causes)	15	13	
number of deaths resulting from adverse events	1	0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 32 (12.50%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	0 / 32 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm I	Arm II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	20 / 20 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lymphoedema			

subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Axillary pain			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Chest pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
Chills			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	26 / 32 (81.25%)	15 / 20 (75.00%)	
occurrences (all)	41	33	
General physical health deterioration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Generalised oedema			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injection site reaction			

subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	1 / 32 (3.13%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 20 (15.00%)	
occurrences (all)	1	7	
Oedema			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	5 / 32 (15.63%)	7 / 20 (35.00%)	
occurrences (all)	5	7	
Pain			
subjects affected / exposed	1 / 32 (3.13%)	5 / 20 (25.00%)	
occurrences (all)	1	9	
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Thirst			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Xerosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 32 (12.50%)	4 / 20 (20.00%)	
occurrences (all)	4	5	
Dyspnoea			

subjects affected / exposed	6 / 32 (18.75%)	8 / 20 (40.00%)	
occurrences (all)	6	10	
Epistaxis			
subjects affected / exposed	1 / 32 (3.13%)	4 / 20 (20.00%)	
occurrences (all)	1	5	
Nasal congestion			
subjects affected / exposed	3 / 32 (9.38%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 32 (15.63%)	3 / 20 (15.00%)	
occurrences (all)	6	3	
Depression			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Hallucination			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	5 / 32 (15.63%)	3 / 20 (15.00%)	
occurrences (all)	5	3	

Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Neutrophil count			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	8 / 32 (25.00%)	2 / 20 (10.00%)	
occurrences (all)	8	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 32 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Pericardial effusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	5 / 32 (15.63%)	3 / 20 (15.00%)	
occurrences (all)	5	3	
Dysgeusia			
subjects affected / exposed	8 / 32 (25.00%)	4 / 20 (20.00%)	
occurrences (all)	11	7	
Headache			
subjects affected / exposed	5 / 32 (15.63%)	5 / 20 (25.00%)	
occurrences (all)	5	5	
Hypoaesthesia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Lethargy			
subjects affected / exposed	0 / 32 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	5	
Memory impairment			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Paraesthesia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Somnolence			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Tremor			

subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	4	2	
Thrombocytopenia			
subjects affected / exposed	7 / 32 (21.88%)	4 / 20 (20.00%)	
occurrences (all)	8	5	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Ocular hyperaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 32 (9.38%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Abdominal pain upper			
subjects affected / exposed	4 / 32 (12.50%)	2 / 20 (10.00%)	
occurrences (all)	5	2	
Constipation			

subjects affected / exposed	12 / 32 (37.50%)	5 / 20 (25.00%)	
occurrences (all)	26	14	
Diarrhoea			
subjects affected / exposed	25 / 32 (78.13%)	15 / 20 (75.00%)	
occurrences (all)	90	61	
Dry mouth			
subjects affected / exposed	4 / 32 (12.50%)	4 / 20 (20.00%)	
occurrences (all)	4	4	
Dyspepsia			
subjects affected / exposed	3 / 32 (9.38%)	4 / 20 (20.00%)	
occurrences (all)	3	11	
Faecal incontinence			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Glossodynia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haemmorrhoids			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Mouth ulceration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Nausea			

subjects affected / exposed	28 / 32 (87.50%)	16 / 20 (80.00%)	
occurrences (all)	83	52	
Reflux gastritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sensitivity of teeth			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	6 / 32 (18.75%)	1 / 20 (5.00%)	
occurrences (all)	6	1	
Tongue ulceration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	24 / 32 (75.00%)	11 / 20 (55.00%)	
occurrences (all)	47	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 32 (15.63%)	3 / 20 (15.00%)	
occurrences (all)	5	4	
Dermatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	3 / 32 (9.38%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Ecchymosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Nail disorder			
subjects affected / exposed	3 / 32 (9.38%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pigmentation disorder			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	3 / 32 (9.38%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Skin exfoliation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin mass			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	3 / 32 (9.38%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Back pain			

subjects affected / exposed	6 / 32 (18.75%)	5 / 20 (25.00%)	
occurrences (all)	6	5	
Bone pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Groin pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	4 / 32 (12.50%)	3 / 20 (15.00%)	
occurrences (all)	5	15	
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 32 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Musculoskeletal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	2 / 32 (6.25%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Pain in extremity			
subjects affected / exposed	4 / 32 (12.50%)	5 / 20 (25.00%)	
occurrences (all)	4	5	
Pain in jaw			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cholecystitis infective			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Injection site infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	6	
Oral herpes			
subjects affected / exposed	0 / 32 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	2 / 32 (6.25%)	2 / 20 (10.00%)	
occurrences (all)	2	2	

Vaginal infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	14 / 32 (43.75%)	10 / 20 (50.00%)	
occurrences (all)	17	13	
Dehydration			
subjects affected / exposed	4 / 32 (12.50%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Hyperglycaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	3 / 32 (9.38%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2009	Amendment 2 was prepared to implement the Urgent Safety Measures in terms of study drug administration which included: 1. Dosing schedule modification: the dosing schedule was modified to an every other week (QOW) dosing with a cycle length of 28 days. For patients who were well tolerating reduced doses, dose re-escalation was also allowed in order to seek maximal clinical benefit from panobinostat. 2. Administration of panobinostat with food: the results of another study, [CLBH589B2111], indicate that panobinostat could be administered without regard to food. These findings were consistent with the results from an earlier pilot food effect [CLBH589B2101] study where it was even recommended to take food with panobinostat as it helps decreasing GI toxicities. 3. Modifications of the ECG schedule: based on updated data from other panobinostat clinical trials, protocol amendment 2 reduced the cardiac monitoring of this study and thus reduced the number of ECGs that were needed to be performed during the course of the study. 4. Patient population extension: all participating sites were contacted iregarding the slow enrollment rate. The contacted investigators indicated that they would favor inclusion of arm I patients with up to two prior cytotoxic chemotherapy in the metastatic setting as there was a medical need for this patient population. Amendment 2 extended the patient population and allowed ER+ and/or PgR+ patients with 2 lines of prior cytotoxic chemotherapy in the metastatic setting to be eligible for the trial.
16 September 2010	Protocol amendment 3, included the following: 1. Closure of enrollment in Arm II: In Arm II (the ER- and PgR- patient population), accrual was slower than anticipated and the required number of evaluable patients had not been reached in stage I (only one partial response had been observed in the ongoing patients). Because of the very low patient enrollment and because the Risks to Benefit ratio seen thus far did not justify the accrual of more patients in this arm, a decision was made to close this study arm for enrollment. The patients already included were given the possibility to continue in the study. It was worth noting that in Arm I (the ER+ and/or PgR+ patient population), the enrollment was temporarily closed as per protocol as the first cohort was enrolled and the number of responses required to open stage II was not reached (only one response was observed whereas three were required to open stage II). 2. Follow-up: because of the small number of patients registered in the study (premature end of study arm II, and stage II not opened for arm I), the survival information would not have provided information that would have been relevant for the patients and for panobinostat development. For this reason, the follow-up part of the protocol was removed and the patients were not followed after their End-of-Study visit. 3. Secondary and exploratory objectives of the study: with such a small number of patients registered in the study, independent central review of the scans would not have provided statistically relevant information, nor would the assessment of progression-free survival, time to response, duration of response, overall survival, or the confirmation of the patients' status of HER2, Estrogen Receptors and Progesterone Receptors by a central laboratory. These three objectives and their corresponding endpoints were therefore removed from the protocol. The exploratory objective performed on core needle biopsy was also removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 September 2010	The study was not specifically interupted rather as specified under Protocol 3, enrollment in Arm II was closed due to a decision made after a Steering Committee Meeting held on 7 July 2010 to review the efficacy and safety data of the study. Based on slower than anticipated patient accrual and an unfavourable Risk to Benfit ratio, it was no longer justified to aquire more patients. It is important to note that the patients already included were given the possibility to continue, and therefore no interruption in the study.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In Arm II, enrollment was discontinued due to low recruitment, resulting in insufficient data to determine efficacy. In Arm I, the required number of tumour responses was not achieved. The sample size was too small to analyze secondary objectives.

Notes: