



## 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                                                                        |
| Sponsor organisation address | Suite 1100 9925-109 Street , Edmonton, Canada, T5K 2J8                                                    |
| Public contact               | Valérie Bee-Munteanu, Translational Research in Oncology, +33(1) 58 10 09 09, valerie.bee@trioncology.org |
| Scientific contact           | Valérie Bee-Munteanu, Translational Research in Oncology, +33(1) 58 10 09 09, valerie.bee@trioncology.org |

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   |
| <b>Arm title</b>             | 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.

|                  |        |
|------------------|--------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b>             | 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<br>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<br>Units: years                     |                                  |                   |                      |
| arithmetic mean                                    | 57.4                             | 58.1              |                      |
| standard deviation                                 | ± 10.5                           | ± 9.8             | ±                    |
| Gender categorical<br>Units: Subjects              |                                  |                   |                      |
| Female                                             | 54                               | 52                |                      |
| Male                                               | 0                                | 0                 |                      |
| Menopausal Status<br>Units: Subjects               |                                  |                   |                      |
| Premenopausal                                      | 5                                | 4                 |                      |
| Postmenopausal                                     | 49                               | 48                |                      |
| Race<br>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:<br>Hormone receptor positive (estrogen and/or progesterone receptor positive), HER2-negative.                                                                                                                                                                                                                                                                   |                                  |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                        | Arm II                           |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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 assessment). The timeframe was defined as follows: <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul> (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:<br>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  $H_0: r \leq 4\%$  against  $H_A: r \geq 16\%$  (where  $r$  is the response rate)
- type I error rate ( $\alpha$ , probability of accepting ineffective treatment, a false positive outcome) is set to 5%
- type II error rate ( $\beta$ , 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 <sup>[1]</sup> |
| 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          |  |
| <b>Blood and lymphatic system disorders</b>                 |                 |                |  |
| <b>Anaemia</b>                                              |                 |                |  |
| 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          |  |
| <b>Neutropenia</b>                                          |                 |                |  |
| 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          |  |
| <b>Thrombocytopenia</b>                                     |                 |                |  |
| 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          |  |
| <b>General disorders and administration site conditions</b> |                 |                |  |
| <b>Fatigue</b>                                              |                 |                |  |
| 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          |  |
| <b>General physical health deterioration</b>                |                 |                |  |
| 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          |  |
| <b>Gastrointestinal disorders</b>                           |                 |                |  |
| <b>Abdominal discomfort</b>                                 |                 |                |  |
| 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          |  |
| <b>Ascites</b>                                              |                 |                |  |
| 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          |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |  |
| 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          |  |
| <b>Metabolism and nutrition disorders</b>              |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Arm I             | Arm II            |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 32 / 32 (100.00%) | 20 / 20 (100.00%) |  |
| <b>Vascular disorders</b>                             |                   |                   |  |
| 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<br>occurrences (all)                                                                                            | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Surgical and medical procedures<br>Tooth extraction<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| General disorders and administration<br>site conditions<br>Application site haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                                                                                | 1 / 32 (3.13%)<br>1    | 2 / 20 (10.00%)<br>2   |  |
| Axillary pain<br>subjects affected / exposed<br>occurrences (all)                                                                           | 1 / 32 (3.13%)<br>1    | 1 / 20 (5.00%)<br>1    |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                                                                              | 1 / 32 (3.13%)<br>2    | 3 / 20 (15.00%)<br>3   |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                                                                                  | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                                                 | 26 / 32 (81.25%)<br>41 | 15 / 20 (75.00%)<br>33 |  |
| General physical health deterioration<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Generalised oedema<br>subjects affected / exposed<br>occurrences (all)                                                                      | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)                                                                  | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>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<br>occurrences (all) | 2 / 32 (6.25%)<br>2 | 0 / 20 (0.00%)<br>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                |
| Haemorrhoids                     |                  |                  |
| 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 erythrodysesthesia 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<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>2    |  |
| Metabolism and nutrition disorders                                                          |                        |                        |  |
| Appetite disorder<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 32 (3.13%)<br>1    | 1 / 20 (5.00%)<br>1    |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 14 / 32 (43.75%)<br>17 | 10 / 20 (50.00%)<br>13 |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 32 (12.50%)<br>4   | 1 / 20 (5.00%)<br>1    |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 32 (9.38%)<br>3    | 2 / 20 (10.00%)<br>2   |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 32 (0.00%)<br>0    | 1 / 20 (5.00%)<br>1    |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 32 (0.00%)<br>0    | 2 / 20 (10.00%)<br>3   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 September 2009 | <p>Amendment 2 was prepared to implement the Urgent Safety Measures in terms of study drug administration which included:</p> <ol style="list-style-type: none"><li>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.</li><li>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.</li><li>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.</li><li>4. Patient population extension: all participating sites were contacted regarding 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.</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 16 September 2010 | <p>Protocol amendment 3, included the following:</p> <ol style="list-style-type: none"><li>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.<br/>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).</li><li>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.</li><li>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.<br/>The exploratory objective performed on core needle biopsy was also removed.</li></ol> |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date              | Interruption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Restart date |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 16 September 2010 | <p>The study was not specifically interrupted 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 Benefit ratio, it was no longer justified to acquire more patients.</p> <p>It is important to note that the patients already included were given the possibility to continue, and therefore no interruption in the study.</p> | -            |

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: