



## Clinical trial results:

**Phase III trial of IV vinflunine versus an alkylating agent in patients with metastatic breast cancer previously treated with or resistant to an anthracycline, a taxane, an antimetabolite, and a vinca-alkaloid (study L00070 IN 308 B0)**

### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2009-011118-47                |
| Trial protocol           | FR PT IT ES BE DE AT HU GB BG |
| Global end of trial date | 17 January 2014               |

### Results information

|                                |                                                                                                                                                                    |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                                                       |
| This version publication date  | 20 June 2019                                                                                                                                                       |
| First version publication date | 08 January 2017                                                                                                                                                    |
| Version creation reason        | <ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Update of safety data of subjects still ongoing treatment at the primary cut-off |

### Trial information

#### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | L00070 IN 3 08 B0 |
|-----------------------|-------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01091168 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | PIERRE FABRE MEDICAMENT                                                                                                                |
| Sponsor organisation address | 45, place Abel Gance, Boulogne Billancourt, France,                                                                                    |
| Public contact               | Dr Karim Keddad, INSTITUT DE RECHERCHE PIERRE FABRE, karim.keddad@pierre-fabre.com                                                     |
| Scientific contact           | Dr Karim Keddad, Centre de Recherche et Développement clinique. 3 avenue Hubert CURIEN - 31000 TOULOUSE, karim.keddad@pierre-fabre.com |

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 August 2012  |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 27 August 2012  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 January 2014 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To compare the overall survival in patients treated with i.v. vinflunine versus those receiving an alkylating agent of physician's choice.

Protection of trial subjects:

Antiemetic (corticosteroids) in both arms

Laxatives in test drug arm

All best supportive treatment: analgesics for pain, biphosphonates for bone metastasis localized radiotherapy in case of bone pain, transfusion, erythropoietin, GCSF in case of neutropenia gr 4 lasting at least 7 days or febrile neutropenia or neutropenic infection and then prophylactically in further cycles

Background therapy:

Antiemetic (corticosteroids) in both arms

Laxatives in test drug arm

All best supportive treatment: analgesics for pain, biphosphonates for bone metastasis, localized radiotherapy in case of bone pain, transfusion, erythropoietin, GCSF in case of neutropenia gr 4 lasting at least 7 days or febrile neutropenia or neutropenic infection and then prophylactically in further cycles

Evidence for comparator:

Alkylating agents (cyclophosphamide, carboplatin, cisplatin, melphalan, thiotepa, mitomycin C) are according to investigators acceptable treatment MBC in patients having exhausted the most active cytotoxics because they have shown some activity in this setting

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 15 July 2009     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 5 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 15          |
| Country: Number of subjects enrolled | Brazil: 13             |
| Country: Number of subjects enrolled | Mexico: 13             |
| Country: Number of subjects enrolled | South Africa: 7        |
| Country: Number of subjects enrolled | Taiwan: 26             |
| Country: Number of subjects enrolled | Belarus: 54            |
| Country: Number of subjects enrolled | Russian Federation: 57 |
| Country: Number of subjects enrolled | Serbia: 3              |
| Country: Number of subjects enrolled | Ukraine: 10            |
| Country: Number of subjects enrolled | Poland: 37             |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Portugal: 4        |
| Country: Number of subjects enrolled | Spain: 78          |
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | Austria: 10        |
| Country: Number of subjects enrolled | Belgium: 6         |
| Country: Number of subjects enrolled | Bulgaria: 3        |
| Country: Number of subjects enrolled | France: 162        |
| Country: Number of subjects enrolled | Germany: 24        |
| Country: Number of subjects enrolled | Hungary: 2         |
| Country: Number of subjects enrolled | Italy: 54          |
| Worldwide total number of subjects   | 594                |
| EEA total number of subjects         | 396                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 463 |
| From 65 to 84 years                       | 131 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was randomized on 15 July 2009 and the last patient was randomized on 11 October 2011. The recruitment period lasted 27 months. A total of 594 patients with metastatic breast cancer were randomized in the study in 130 sites over 20 countries.

### Pre-assignment

Screening details:

Inclusion criteria included: women  $\geq 18$  years and  $\leq 75$  years, with histologically or cytologically confirmed breast cancer; at least two prior chemotherapy regimens for the treatment of locally recurrent and/or metastatic disease excluding chemotherapy received in the neo/adjuvant setting; prior treatment included an anthracycline (A), a taxane (T)

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 594 |
| Number of subjects completed | 594 |

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall period (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Not blinded                     |

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Vinflunine |

Arm description:

vinflunine 280 mg/m<sup>2</sup>/day on day 1 of a 3 week cycle

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Vinflunine                                       |
| Investigational medicinal product code | L0070                                            |
| Other name                             | Javlor®                                          |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

280 mg/m<sup>2</sup>/day on day 1 of each 3 weeks cycle, over a 20-minute intravenous (IV) infusion

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Alkylating agent |
|------------------|------------------|

Arm description:

alkylating agent of physician choice

|                                        |                                                                                      |
|----------------------------------------|--------------------------------------------------------------------------------------|
| Arm type                               | Active comparator                                                                    |
| Investigational medicinal product name | cyclophosphamide or cisplatin or carboplatin or thiotepa or melphalan or mitomycin C |
| Investigational medicinal product code |                                                                                      |
| Other name                             |                                                                                      |
| Pharmaceutical forms                   | Buccal tablet, Solution for injection/infusion                                       |
| Routes of administration               | Buccal use, Intravenous use                                                          |

Dosage and administration details:

All comparator drugs were commercially available and approved for the treatment of cancer in the country where they were used. Alkylating agents which were received as single agent every 3 weeks, included cyclophosphamide (IV or oral), melphalan (IV or oral), mitomycin C, thiotepa, cisplatin and carboplatin according to SPCs

| <b>Number of subjects in period 1</b> | Vinflunine | Alkylating agent |
|---------------------------------------|------------|------------------|
| Started                               | 298        | 296              |
| cut-off date                          | 243        | 229              |
| Completed                             | 0          | 0                |
| Not completed                         | 298        | 296              |
| Consent withdrawn by subject          | 1          | 3                |
| Physician decision                    | 15         | 12               |
| Adverse event, non-fatal              | 21         | 24               |
| Other                                 | 2          | -                |
| progressive disease                   | 250        | 234              |
| Lost to follow-up                     | -          | 1                |
| patient's decision                    | 9          | 20               |
| Protocol deviation                    | -          | 2                |

## Baseline characteristics

### Reporting groups

|                                                                                     |                  |
|-------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                               | Vinflunine       |
| Reporting group description:<br>vinflunine 280 mg/m2/day on day 1 of a 3 week cycle |                  |
| Reporting group title                                                               | Alkylating agent |
| Reporting group description:<br>alkylating agent of physician choice                |                  |

| Reporting group values                             | Vinflunine | Alkylating agent | Total |
|----------------------------------------------------|------------|------------------|-------|
| Number of subjects                                 | 298        | 296              | 594   |
| Age categorical<br>Units: Subjects                 |            |                  |       |
| Adults (18-64 years)                               | 236        | 227              | 463   |
| From 65-84 years                                   | 62         | 69               | 131   |
| 85 years and over                                  | 0          | 0                | 0     |
| Age continuous<br>Units: years                     |            |                  |       |
| geometric mean                                     | 57.2       | 56.5             | -     |
| standard deviation                                 | ± 9.1      | ± 10.2           | -     |
| Gender categorical<br>Units: Subjects              |            |                  |       |
| Female                                             | 298        | 296              | 594   |
| WHO Performance status<br>Units: Subjects          |            |                  |       |
| WHO 0                                              | 103        | 110              | 213   |
| WHO 1                                              | 164        | 155              | 319   |
| WHO 2                                              | 31         | 31               | 62    |
| Menopausal status<br>Units: Subjects               |            |                  |       |
| Menopausal                                         | 237        | 211              | 448   |
| Non Menaopausal                                    | 61         | 85               | 146   |
| Main histopathological type<br>Units: Subjects     |            |                  |       |
| Ductal                                             | 220        | 220              | 440   |
| Lobular                                            | 25         | 28               | 53    |
| Carcinoma NOS                                      | 36         | 38               | 74    |
| Others                                             | 17         | 10               | 27    |
| Time from diagnosis to study entry<br>Units: years |            |                  |       |
| median                                             | 1.2        | 1.3              | -     |
| full range (min-max)                               | 0 to 9.8   | 0 to 10.7        | -     |

## End points

### End points reporting groups

|                                                                  |                  |
|------------------------------------------------------------------|------------------|
| Reporting group title                                            | Vinflunine       |
| Reporting group description:                                     |                  |
| vinflunine 280 mg/m <sup>2</sup> /day on day 1 of a 3 week cycle |                  |
| Reporting group title                                            | Alkylating agent |
| Reporting group description:                                     |                  |
| alkylating agent of physician choice                             |                  |

### Primary: Overall Survival (OS)

|                                                         |                       |
|---------------------------------------------------------|-----------------------|
| End point title                                         | Overall Survival (OS) |
| End point description:                                  |                       |
| OS was defined as the time from randomisation to death. |                       |
| End point type                                          | Primary               |
| End point timeframe:                                    |                       |
| from Baseline to cut-off date (August, 27 th 2012)      |                       |

| End point values                 | Vinflunine        | Alkylating agent  |  |  |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed      | 298               | 296               |  |  |
| Units: months                    |                   |                   |  |  |
| median (confidence interval 95%) | 9.1 (7.7 to 10.4) | 9.3 (7.5 to 10.9) |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                               |                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                    | Primary efficacy analysis     |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                             |                               |
| Kaplan-Meier curves and life tables by treatment arm were provided. Confidence intervals on the median were calculated using the Brookmeyer and Crowley method. Hazard ratio and 95% confidence intervals were reported. A stratified Cox proportional model was performed to compare the two treatment arms taking into account the stratification factors (except centre) used at the time of randomisation |                               |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                             | Alkylating agent v Vinflunine |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                       | 594                           |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                        | Pre-specified                 |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                 | superiority <sup>[1]</sup>    |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                       | = 0.673 <sup>[2]</sup>        |
| Method                                                                                                                                                                                                                                                                                                                                                                                                        | Cochran-Mantel-Haenszel       |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                            | Hazard ratio (HR)             |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                | 1.04                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.86    |
| upper limit         | 1.25    |

Notes:

[1] - As a secondary analysis of the OS, a Multivariate analysis was conducted in the ITT population using the Cox proportional hazard model to estimate the simultaneous effect of the following prognosis factors: age, number of organs involved, time from initial diagnosis to randomisation, prior hormonal therapy, prior neo/adjuvant chemotherapy, hormone receptors and Her-2 status.

The only prognostic factor which was significant was the number of organs involved :  $P < 0.0001$  when the number was  $> 2$

[2] - The median OS was similar in the 2 study arms : 9.1 months in the VFL arm and 9.3 months in the anti alkylating agents arm (HR = 1.04, 95% CI = 0.86 - 1.25,  $P = 0.6730$ )

## Secondary: Progression Free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression Free Survival |
|-----------------|---------------------------|

End point description:

PFS was defined as the time from randomisation to the first tumour progression or death due to any cause in the absence of previous documentation of objective tumour progression. PFS was performed in the ITT and eligible populations. For patients lost of follow up, or without a known record of progression or death, PFS was censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression which ever occurred last

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to cut-off date

| End point values                 | Vinflunine         | Alkylating agent   |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 298 <sup>[3]</sup> | 296 <sup>[4]</sup> |  |  |
| Units: months                    |                    |                    |  |  |
| median (confidence interval 95%) | 2.5 (1.7 to 2.7)   | 1.9 (1.5 to 2.6)   |  |  |

Notes:

[3] - 291 events-7 censored

[4] - 286 events-10 censored

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | PFS secondary analysis |
|----------------------------|------------------------|

Statistical analysis description:

PFS was compared between the 2 treatment arms by the log-rank test procedure with the 5 % significant level, stratified on the stratification factors (except study site) as specified at the time of randomisation. OS was analysed using Kaplan-Meier method and summarized with median and 95% CI of the median

|                   |                               |
|-------------------|-------------------------------|
| Comparison groups | Vinflunine v Alkylating agent |
|-------------------|-------------------------------|

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 594                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.4927 <sup>[5]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.94                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.8                     |
| upper limit                             | 1.12                    |

Notes:

[5] - Investigator-assessed median PFS was slightly longer in the VFL arm without statistically significant difference : 2.5 months in the VFL arm and 1.9 months in the AA arm, p=0.4927

## Secondary: Disease Control Rate

|                                                                                                                                                         |                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point title                                                                                                                                         | Disease Control Rate |
| End point description:                                                                                                                                  |                      |
| DCR was defined as the proportion of patients with CR, PR and stable disease (SD), relative to the total number of patients in the analysed population. |                      |
| End point type                                                                                                                                          | Secondary            |
| End point timeframe:                                                                                                                                    |                      |
| From baseline to cut-off date                                                                                                                           |                      |

| End point values                 | Vinflunine          | Alkylating agent  |  |  |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type               | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed      | 298                 | 296               |  |  |
| Units: percent                   |                     |                   |  |  |
| median (confidence interval 95%) | 43.6 (37.9 to 49.3) | 35.5 (30 to 41.2) |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                             |                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                  | DCR: Secondary efficacy analysis |
| Statistical analysis description:                                                                                                                                                                                                                                                                                           |                                  |
| the disease control rate (DCR) were compared in the ITT population and in the population evaluable for response between the 2 arms with a cochrane Mantel Haenszel, stratified on WHO performance status at baseline, number of prior chemotherapy lines for the treatment of disease and disease measurability at baseline |                                  |
| Comparison groups                                                                                                                                                                                                                                                                                                           | Vinflunine v Alkylating agent    |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                     | 594                              |
| Analysis specification                                                                                                                                                                                                                                                                                                      | Pre-specified                    |
| Analysis type                                                                                                                                                                                                                                                                                                               | superiority                      |
| P-value                                                                                                                                                                                                                                                                                                                     | = 0.0424 <sup>[6]</sup>          |
| Method                                                                                                                                                                                                                                                                                                                      | Logrank                          |

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Notes:

[6] - Disease control rates (DCRs) were significantly higher in the Vinflunine arm compared to the AA arm whatever the population considered. In the ITT population, DCRs were 43.6% in the VFL arm and 35.5% in the AA arm ( $P = 0.0424$ ).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

TEAEs are reported from time of first dose of study treatment up to 30 days after last dose of study treatment at the exception of SAEs occurred after discontinuation and start of a further treatment.

Adverse event reporting additional description:

The same event may appear as both an AE and SAE. However what is presented are distinct events. An event may be categorized as serious in 1 subject and as non serious in another. Specific AE tables were generated separately as per EU format. We report here all "on study" SAEs and treatment related AEs by SOC and PT (PT ≥ 1%)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 12.0   |

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Alkylating agent |
|-----------------------|------------------|

Reporting group description:

alkylating agent of physician choice

|                       |            |
|-----------------------|------------|
| Reporting group title | Vinflunine |
|-----------------------|------------|

Reporting group description:

vinflunine 280 mg/m<sup>2</sup>/day on day 1 of a 3-week cycle

| Serious adverse events                                              | Alkylating agent  | Vinflunine        |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 66 / 290 (22.76%) | 82 / 297 (27.61%) |  |
| number of deaths (all causes)                                       | 229               | 243               |  |
| number of deaths resulting from adverse events                      | 0                 | 1                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Malignant neoplasm progression                                      |                   |                   |  |
| subjects affected / exposed                                         | 43 / 290 (14.83%) | 38 / 297 (12.79%) |  |
| occurrences causally related to treatment / all                     | 0 / 43            | 0 / 38            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Cancer pain                                                         |                   |                   |  |
| subjects affected / exposed                                         | 0 / 290 (0.00%)   | 1 / 297 (0.34%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| squamous cell carcinoma                                             |                   |                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 290 (0.00%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue                                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 290 (0.00%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Pulmonary embolism                                   |                 |                 |  |
| subjects affected / exposed                          | 2 / 290 (0.69%) | 4 / 297 (1.35%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 1 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 1 / 1           |  |
| Dyspnoea                                             |                 |                 |  |
| subjects affected / exposed                          | 2 / 290 (0.69%) | 6 / 297 (2.02%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 7           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 290 (0.34%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                            |                 |                 |  |
| subjects affected / exposed                          | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hallucination                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Transaminases increased                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Allergic transfusion reaction                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Arteriospasm coronary                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Epilepsy                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuralgia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brachial plexopathy                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral sensory neuropathy                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 6 / 297 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 9 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 6 / 297 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 9 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 3 / 297 (1.01%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 290 (0.69%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis staphylococcal                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 5 / 297 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 290 (1.03%) | 6 / 297 (2.02%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 4 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 4 / 297 (1.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 3 / 297 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 3 / 297 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 3 / 297 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal Stenosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Myalgia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone Pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Neutropenic infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 4 / 297 (1.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumoniae                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 3 / 297 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 290 (0.69%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| influenza                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Catheter related infection                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central line infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 290 (0.00%) | 2 / 297 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 290 (0.34%) | 1 / 297 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 290 (0.34%) | 0 / 297 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Alkylating agent   | Vinflunine         |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 262 / 290 (90.34%) | 197 / 297 (66.33%) |  |
| Investigations                                        |                    |                    |  |
| Weight decreased                                      |                    |                    |  |
| subjects affected / exposed                           | 17 / 290 (5.86%)   | 26 / 297 (8.75%)   |  |
| occurrences (all)                                     | 23                 | 34                 |  |
| Nervous system disorders                              |                    |                    |  |
| Peripheral sensory neuropathy                         |                    |                    |  |
| subjects affected / exposed                           | 5 / 290 (1.72%)    | 21 / 297 (7.07%)   |  |
| occurrences (all)                                     | 9                  | 48                 |  |
| Headache                                              |                    |                    |  |
| subjects affected / exposed                           | 5 / 290 (1.72%)    | 7 / 297 (2.36%)    |  |
| occurrences (all)                                     | 7                  | 15                 |  |
| Dizziness                                             |                    |                    |  |
| subjects affected / exposed                           | 4 / 290 (1.38%)    | 3 / 297 (1.01%)    |  |
| occurrences (all)                                     | 7                  | 4                  |  |
| General disorders and administration site conditions  |                    |                    |  |
| Asthenia                                              |                    |                    |  |
| subjects affected / exposed                           | 43 / 290 (14.83%)  | 89 / 297 (29.97%)  |  |
| occurrences (all)                                     | 62                 | 177                |  |
| Injection site reaction                               |                    |                    |  |
| subjects affected / exposed                           | 2 / 290 (0.69%)    | 29 / 297 (9.76%)   |  |
| occurrences (all)                                     | 2                  | 58                 |  |
| Fatigue                                               |                    |                    |  |
| subjects affected / exposed                           | 25 / 290 (8.62%)   | 23 / 297 (7.74%)   |  |
| occurrences (all)                                     | 35                 | 55                 |  |
| Pain                                                  |                    |                    |  |
| subjects affected / exposed                           | 0 / 290 (0.00%)    | 4 / 297 (1.35%)    |  |
| occurrences (all)                                     | 0                  | 4                  |  |

|                                                                          |                          |                           |  |
|--------------------------------------------------------------------------|--------------------------|---------------------------|--|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 3 / 290 (1.03%)<br>5     | 10 / 297 (3.37%)<br>19    |  |
| Blood and lymphatic system disorders                                     |                          |                           |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)          | 31 / 290 (10.69%)<br>46  | 37 / 297 (12.46%)<br>56   |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)     | 39 / 290 (13.45%)<br>64  | 3 / 297 (1.01%)<br>3      |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 6 / 290 (2.07%)<br>9     | 2 / 297 (0.67%)<br>2      |  |
| Gastrointestinal disorders                                               |                          |                           |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 23 / 290 (7.93%)<br>34   | 102 / 297 (34.34%)<br>181 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 67 / 290 (23.10%)<br>126 | 70 / 297 (23.57%)<br>131  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 16 / 290 (5.52%)<br>58   | 66 / 297 (22.22%)<br>170  |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 18 / 290 (6.21%)<br>23   | 52 / 297 (17.51%)<br>98   |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 33 / 290 (11.38%)<br>45  | 34 / 297 (11.45%)<br>44   |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 19 / 290 (6.55%)<br>35   | 16 / 297 (5.39%)<br>24    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 4 / 290 (1.38%)<br>5     | 14 / 297 (4.71%)<br>24    |  |
| Abdominal distension                                                     |                          |                           |  |

|                                                                  |                       |                         |  |
|------------------------------------------------------------------|-----------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                 | 1 / 290 (0.34%)<br>1  | 5 / 297 (1.68%)<br>5    |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 290 (0.34%)<br>1  | 4 / 297 (1.35%)<br>4    |  |
| gastritis<br>subjects affected / exposed<br>occurrences (all)    | 0 / 290 (0.00%)<br>0  | 4 / 297 (1.35%)<br>4    |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all) | 0 / 290 (0.00%)<br>0  | 4 / 297 (1.35%)<br>3    |  |
| Skin and subcutaneous tissue disorders                           |                       |                         |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)     | 9 / 290 (3.10%)<br>12 | 30 / 297 (10.10%)<br>31 |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)     | 2 / 290 (0.69%)<br>1  | 7 / 297 (2.36%)<br>11   |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)     | 3 / 290 (1.03%)<br>3  | 4 / 297 (1.35%)<br>4    |  |
| Psychiatric disorders                                            |                       |                         |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 290 (0.00%)<br>0  | 10 / 297 (3.37%)<br>18  |  |
| Musculoskeletal and connective tissue disorders                  |                       |                         |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)      | 5 / 290 (1.72%)<br>5  | 38 / 297 (12.79%)<br>78 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 290 (1.03%)<br>3  | 21 / 297 (7.07%)<br>53  |  |
| Pain in Jaw<br>subjects affected / exposed<br>occurrences (all)  | 0 / 290 (0.00%)<br>0  | 12 / 297 (4.04%)<br>24  |  |
| Muscle spasms                                                    |                       |                         |  |

|                                                                                                    |                        |                         |  |
|----------------------------------------------------------------------------------------------------|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                   | 2 / 290 (0.69%)<br>2   | 6 / 297 (2.02%)<br>6    |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 290 (0.34%)<br>1   | 4 / 297 (1.35%)<br>8    |  |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all) | 24 / 290 (8.28%)<br>29 | 31 / 297 (10.44%)<br>62 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 May 2009       | The extra label on the commercial packaging of the alkylating agent used as comparator drugs was deleted.<br>The HER2 and hormonal receptors status was required to be obtained at baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 23 September 2009 | The use of GCSF had to follow local (Taiwan) guidelines and medical practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 15 December 2009  | <ul style="list-style-type: none"><li>- Inclusion criterion n°4: the upper limit of number of prior chemotherapy lines (no more than 5) was deleted because approximatively 1/3 of screened patients were found ineligible</li><li>- Inclusion criterion n° 9: the delay between discontinuation of anti HER2 targeted therapy was shortened from 4 to 3 weeks as far as no additional toxicity was expected</li><li>- Inclusion criterion n° 10: the delay between discontinuation of radiation therapy was shortened from 4 to 3 weeks because only localised palliative radiotherapy was performed at this far advanced stage of breast cancer</li><li>- Inclusion criterion n° 15: To add as prohibited treatment during the month preceding first study drug administration,transfusions except if medically indicated</li><li>- Exclusion criterion n° 1: symptomatic ascites (grade <math>\geq 2</math>) requiring active treatment was added</li></ul> <p>To adapt the stratification factor concerning the number of prior lines for the treatment of locally recurrent/metastatic disease excluding chemotherapy given in the neo/adjuvant setting.</p> <p>To add complementary information to vinflunine reconstitution procedure (possibility to use G5% solution)</p> <p>To modify restriction of use of alkylating agents in order to stick to local practice in each countries. (Alkylating agents approved for the treatment of cancer in general in the country and not only in breast cancer were prescribed)</p> <p>To define the cycle for alkylating agent as a 3 week period in order to homogenize periodicity of tumour assessments between the 2 arms</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported