



## Clinical trial results:

**Phase II study evaluating oral vinorelbine as a single agent in patients with hormone receptor breast cancer with bone metastases previously treated by a hormone therapy**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-014497-18 |
| Trial protocol           | FR AT IT ES    |
| Global end of trial date | 17 June 2015   |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 31 January 2019 |
| First version publication date | 31 January 2019 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | PM0259 CA 228 BO |
|-----------------------|------------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                                                             |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Pierre Fabre Médicament                                                                                                                     |
| Sponsor organisation address | 45 place Abel Gance, Boulogne, France, 92100                                                                                                |
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Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 16 March 2015 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 09 May 2013   |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 June 2015  |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To determine the Progression-Free Survival (PFS) of oral vinorelbine as a single agent in patients with hormone receptor positive breast cancer with bone metastases previously treated by a hormone therapy.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study was conducted in compliance with the protocol. The protocol, amendments, and the subject informed consent received Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favourable opinion prior to initiation of the study and/or their implementation.

Background therapy:

Prophylactic oral anti-emetic medication with a 5-HT3 antagonist was recommended before each oral vinorelbine administration. Oral antiemetic treatments were provided to the patients at home. The use of corticosteroids as anti-emetic treatment was allowed. Patients had to receive full supportive care including antibiotics, antidiarrhoeals, analgesics, transfusion of blood products, when appropriate. The use of drugs with laxative properties had to be avoided. Prophylactic use of Colony Stimulating Factor (CSF) was allowed during the study treatment.

Granulocyte stimulating growth factors could be given to patients who experienced febrile neutropenia, grade 4 asymptomatic neutropenia or neutropenic infection according to institutional rules. Patients had to be under treatment by a bisphosphonate since at least one month before entering the study.

Evidence for comparator:

No control arm was planned as the study aimed at evaluating the clinical benefit of oral vinorelbine in patients suffering from bone metastases from breast cancer after failure to hormone therapy.

|                                                           |                                       |
|-----------------------------------------------------------|---------------------------------------|
| Actual start date of recruitment                          | 14 April 2010                         |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Efficacy, Safety, Scientific research |
| Long term follow-up duration                              | 3 Years                               |
| Independent data monitoring committee (IDMC) involvement? | No                                    |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Mexico: 13            |
| Country: Number of subjects enrolled | Russian Federation: 7 |
| Country: Number of subjects enrolled | Poland: 8             |
| Country: Number of subjects enrolled | Spain: 1              |
| Country: Number of subjects enrolled | Austria: 17           |
| Country: Number of subjects enrolled | France: 18            |

|                                      |          |
|--------------------------------------|----------|
| Country: Number of subjects enrolled | Italy: 6 |
| Worldwide total number of subjects   | 70       |
| EEA total number of subjects         | 50       |

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)                      | 46 |
| From 65 to 84 years                       | 24 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 70 patients with hormone receptor positive breast cancer with bone metastases previously treated by a hormone therapy were enrolled and received at least one dose of study treatment.

### Pre-assignment

Screening details:

No further information

### Period 1

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

Blinding implementation details:

The study was an open label non-randomized trial.

### Arms

|           |                 |
|-----------|-----------------|
| Arm title | Vinorelbine arm |
|-----------|-----------------|

Arm description:

Patients were included after written informed consent was obtained and all screening assessments have been performed.

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Vinorelbine   |
| Investigational medicinal product code |               |
| Other name                             | Navelbine     |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Patients received Oral vinorelbine single agent at the dose of 60 mg/m<sup>2</sup> weekly at the first cycle (1 cycle = 4 weeks of treatment) then at the increased dose of 80 mg/m<sup>2</sup> at cycle 2 and subsequent cycles in the absence of a grade 3 or grade 4 neutropenia. Oral vinorelbine was given on days 1, 8, 15 and 22 of a cycle. Patients had to receive at least 3 cycles of treatment unless documented disease progression, unacceptable toxicity or patient refusal. Vinorelbine was supplied as soft capsules that had to be rapidly swallowed with a glass of water without chewing or sucking them. It was recommended to take the capsules with some food. The treatment was administered on an outpatient setting. However, the patient had to return to the hospital at Day 1 of each cycle to receive study drugs at the hospital under the supervision of the investigator. The study medication had to be stored refrigerated (2°C to 8°C) and protected from light in the original closed container.

| Number of subjects in period 1                | Vinorelbine arm |
|-----------------------------------------------|-----------------|
| Started                                       | 70              |
| Completed                                     | 0               |
| Not completed                                 | 70              |
| Maximum benefit                               | 3               |
| Drug related toxicity                         | 5               |
| Documented Progressive disease (radiological) | 45              |

|                            |   |
|----------------------------|---|
| Non-drug related toxicity  | 2 |
| Patient's decision to stop | 9 |
| Investigator decision      | 4 |
| clinical progression       | 2 |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values                                                                                                                                                                       | Treatment period | Total |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------|--|
| Number of subjects                                                                                                                                                                           | 70               | 70    |  |
| Age categorical                                                                                                                                                                              |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| Adults (18-64 years)                                                                                                                                                                         | 46               | 46    |  |
| From 65-84 years                                                                                                                                                                             | 24               | 24    |  |
| 85 years and over                                                                                                                                                                            | 0                | 0     |  |
| Age continuous                                                                                                                                                                               |                  |       |  |
| Units: years                                                                                                                                                                                 |                  |       |  |
| median                                                                                                                                                                                       | 60.6             |       |  |
| full range (min-max)                                                                                                                                                                         | 37.6 to 77.7     | -     |  |
| Gender categorical                                                                                                                                                                           |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| Female                                                                                                                                                                                       | 70               | 70    |  |
| Male                                                                                                                                                                                         | 0                | 0     |  |
| Primary tumor site                                                                                                                                                                           |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| Right breast                                                                                                                                                                                 | 35               | 35    |  |
| Left breast                                                                                                                                                                                  | 34               | 34    |  |
| Bilateral                                                                                                                                                                                    | 1                | 1     |  |
| Hormone receptors status at study entry                                                                                                                                                      |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| Oestrogen positive/ Progesterone positive                                                                                                                                                    | 53               | 53    |  |
| Oestrogen positive/Progesterone negative                                                                                                                                                     | 12               | 12    |  |
| Oestrogen negative/Progesterone positive                                                                                                                                                     | 4                | 4     |  |
| unknown                                                                                                                                                                                      | 1                | 1     |  |
| Karnofsky performance status at baseline                                                                                                                                                     |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| 70%                                                                                                                                                                                          | 4                | 4     |  |
| 80%                                                                                                                                                                                          | 14               | 14    |  |
| 90%                                                                                                                                                                                          | 28               | 28    |  |
| 100%                                                                                                                                                                                         | 24               | 24    |  |
| Metastatic sites at initial diagnosis                                                                                                                                                        |                  |       |  |
| Units: Subjects                                                                                                                                                                              |                  |       |  |
| Bone                                                                                                                                                                                         | 58               | 58    |  |
| Bone + Lymph node                                                                                                                                                                            | 10               | 10    |  |
| Bone + Soft tissue                                                                                                                                                                           | 2                | 2     |  |
| Prior (neo)adjuvant chemotherapy                                                                                                                                                             |                  |       |  |
| Prior chemotherapy was given to 44 patients (62.9%), mainly in the adjuvant setting for 42 patients (60%) and consisted mainly of anthracycline containing regimen in 58.6% of the patients. |                  |       |  |

|                             |            |    |  |
|-----------------------------|------------|----|--|
| Units: Subjects             |            |    |  |
| Yes                         | 44         | 44 |  |
| No                          | 26         | 26 |  |
| Prior endocrine therapy     |            |    |  |
| Units: Subjects             |            |    |  |
| Adjuvant                    | 32         | 32 |  |
| Adjuvant + advanced disease | 23         | 23 |  |
| Advanced disease            | 14         | 14 |  |
| Neoadjuvant + adjuvant      | 1          | 1  |  |
| ECOG PS                     |            |    |  |
| Units: percent              |            |    |  |
| median                      | 90         |    |  |
| full range (min-max)        | 70 to 100  | -  |  |
| Weight                      |            |    |  |
| Units: kg                   |            |    |  |
| median                      | 73         |    |  |
| full range (min-max)        | 45 to 108  | -  |  |
| Body surface area           |            |    |  |
| Units: m <sup>2</sup>       |            |    |  |
| median                      | 1.8        |    |  |
| full range (min-max)        | 1.4 to 2.2 | -  |  |

## End points

### End points reporting groups

|                                                                                                                                                       |                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                                 | Vinorelbine arm |
| Reporting group description:<br>Patients were included after written informed consent was obtained and all screening assessments have been performed. |                 |

### Primary: Progression-free survival

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Progression-free survival <sup>[1]</sup> |
| End point description:<br>PFS was estimated on the ITT population (all treated patients) using Kaplan Meier curves and Confidence intervals on the median PFS were calculated using the reflected method. Patients lost to follow-up, or without a known record of progression or death at the time of analysis had the progression-free survival censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occurred last. |                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Primary                                  |
| End point timeframe:<br>PFS was calculated from the registration date until the date of progression or death due to any cause if no progression was recorded first. Median duration of follow-up at final analysis was 43.3 months.                                                                                                                                                                                                                                              |                                          |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: No statistical analysis can be added because the study is a single-arm study.                                                                                                                                                                                                    |                                          |

| End point values                 | Vinorelbine arm  |  |  |  |
|----------------------------------|------------------|--|--|--|
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 70               |  |  |  |
| Units: months                    |                  |  |  |  |
| median (confidence interval 95%) | 8.2 (5.5 to 9.8) |  |  |  |

|                                   |                                                |
|-----------------------------------|------------------------------------------------|
| <b>Attachments (see zip file)</b> | Kaplan Meier estimates of PFS/Kaplan Meier.png |
|-----------------------------------|------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical benefit rate

|                                                                                                                                                                                        |                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                        | Clinical benefit rate |
| End point description:<br>The clinical benefit rate is defined as the percentage of confirmed CR, confirmed PR and stabilization for at least 24 weeks observed in the ITT population. |                       |
| End point type                                                                                                                                                                         | Secondary             |
| End point timeframe:<br>The clinical benefit rate was evaluated until the date of progression or death due to any cause if no progression was recorded first.                          |                       |

| End point values                 | Vinorelbine arm     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 70                  |  |  |  |
| Units: pourcentage               |                     |  |  |  |
| number (confidence interval 95%) | 55.7 (43.3 to 67.6) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response rate

|                                                                                                                                                                                                                                       |                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                       | Overall response rate |
| End point description:                                                                                                                                                                                                                |                       |
| Overall Response Rate (ORR) was defined as the sum of CR and PR rate (using the best confirmed response recorded from the date of randomisation to the end of treatment) in the ITT population, according to investigator assessment. |                       |
| End point type                                                                                                                                                                                                                        | Secondary             |
| End point timeframe:                                                                                                                                                                                                                  |                       |
| Overall Response Rate (ORR) was evaluated from the randomisation to the end of treatment                                                                                                                                              |                       |

| End point values            | Vinorelbine arm |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 70              |  |  |  |
| Units: patients             |                 |  |  |  |
| Non evaluable               | 3               |  |  |  |
| PR confirmed                | 2               |  |  |  |
| CR not confirmed (SD)       | 1               |  |  |  |
| SD > or = 24 weeks          | 36              |  |  |  |
| SD < 24 weeks               | 15              |  |  |  |
| PD                          | 13              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

**End point description:**

Analyses of Overall Survival were performed with the Kaplan-Meier method. Overall survival of patients lost to follow-up or without a known record of death was censored at the date of last news. At DCO, 38 patients (54%) have died (35 from progression, 3 from other reason and 3 have been lost to follow-up). The remaining 29 patients were still alive.

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

**End point timeframe:**

Overall Survival was evaluated from the date of registration to the date of death due to any cause in the ITT population. Median duration of follow-up at final analysis was 43.3 months.

| End point values                 | Vinorelbine arm     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 70                  |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) | 35.2 (26.8 to 47.1) |  |  |  |

**Attachments (see zip file)**

Kaplan-Meier Survival Time/Kaplan Meier Survival time.png

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of disease control**

|                 |                             |
|-----------------|-----------------------------|
| End point title | Duration of disease control |
|-----------------|-----------------------------|

**End point description:**

The disease control rate (sum of confirmed CR, confirmed PR and stabilisation rate) were evaluated for the ITT population.

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

**End point timeframe:**

The duration of disease control (CR, PR and stabilization of at least 24 weeks) was measured from the date of registration until the criteria for disease progression is met or the date of death or start of new anticancer therapy.

| End point values                 | Vinorelbine arm   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 70                |  |  |  |
| Units: months                    |                   |  |  |  |
| median (confidence interval 95%) | 8.9 (7.3 to 11.1) |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Each patient was assessed for occurrence of AEs throughout the study period (starting after the 1st dose of study medication and up to and including 30 days after the last dose). At DCO, all patients have discontinued (med duration: 5.8 (0.9-18.4)months).

Adverse event reporting additional description:

Any AE occurring during the study period, spontaneously reported by the patient or observed by others, was recorded in the CRF. The relative dose intensity was 83.0% [22.9-108.2]. More than 1/3 of the patients received more than 90% of the planned dose. The median number of cycles was 6 (1-18).

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description: -

| Serious adverse events                            | Safety population |  |  |
|---------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 12 / 70 (17.14%)  |  |  |
| number of deaths (all causes)                     | 0                 |  |  |
| number of deaths resulting from adverse events    | 0                 |  |  |
| Vascular disorders                                |                   |  |  |
| Cerebrovascular accident                          |                   |  |  |
| subjects affected / exposed                       | 1 / 70 (1.43%)    |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Nervous system disorders                          |                   |  |  |
| Monoparesis                                       |                   |  |  |
| subjects affected / exposed                       | 1 / 70 (1.43%)    |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Ischaemic stroke                                  |                   |  |  |
| subjects affected / exposed                       | 1 / 70 (1.43%)    |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Blood and lymphatic system disorders              |                   |  |  |
| Neutropenia                                       |                   |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Neutropenic infection                                |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Upper limb fracture                                  |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Pneumonia                                            |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Ear and labyrinth disorders                          |                |  |  |
| Vertigo                                              |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Eye disorders                                        |                |  |  |
| Cataract                                             |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Optic neuritis                                       |                |  |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Gastritis                                            |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea                                          |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholecystitis acute                             |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Biliary colic                                   |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystectomy                                 |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Musculoskeletal pain                            |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Spinal cord compression                         |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| pulmonary infection                             |                |  |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|                                                       |                   |  |  |
|-------------------------------------------------------|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | Safety population |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 68 / 70 (97.14%)  |  |  |
| Investigations                                        |                   |  |  |
| Weight decreased                                      |                   |  |  |
| subjects affected / exposed                           | 17 / 70 (24.29%)  |  |  |
| occurrences (all)                                     | 70                |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypertension                                          |                   |  |  |
| subjects affected / exposed                           | 5 / 70 (7.14%)    |  |  |
| occurrences (all)                                     | 11                |  |  |
| Nervous system disorders                              |                   |  |  |
| Dizziness                                             |                   |  |  |
| subjects affected / exposed                           | 5 / 70 (7.14%)    |  |  |
| occurrences (all)                                     | 6                 |  |  |
| Headache                                              |                   |  |  |
| subjects affected / exposed                           | 14 / 70 (20.00%)  |  |  |
| occurrences (all)                                     | 28                |  |  |
| Paraesthesia                                          |                   |  |  |
| subjects affected / exposed                           | 6 / 70 (8.57%)    |  |  |
| occurrences (all)                                     | 7                 |  |  |
| Peripheral sensory neuropathy                         |                   |  |  |
| subjects affected / exposed                           | 8 / 70 (11.43%)   |  |  |
| occurrences (all)                                     | 10                |  |  |
| Blood and lymphatic system disorders                  |                   |  |  |
| Anaemia                                               |                   |  |  |
| subjects affected / exposed                           | 58 / 70 (82.86%)  |  |  |
| occurrences (all)                                     | 304               |  |  |
| Neutropenia                                           |                   |  |  |
| subjects affected / exposed                           | 57 / 70 (81.43%)  |  |  |
| occurrences (all)                                     | 243               |  |  |

|                                                                          |                         |  |  |
|--------------------------------------------------------------------------|-------------------------|--|--|
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)     | 12 / 70 (17.14%)<br>24  |  |  |
| General disorders and administration<br>site conditions                  |                         |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)               | 4 / 70 (5.71%)<br>4     |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)              | 40 / 70 (57.14%)<br>116 |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 15 / 70 (21.43%)<br>17  |  |  |
| Gastrointestinal disorders                                               |                         |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 16 / 70 (22.86%)<br>26  |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 10 / 70 (14.29%)<br>13  |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 28 / 70 (40.00%)<br>51  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 38 / 70 (54.29%)<br>99  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 49 / 70 (70.00%)<br>163 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 32 / 70 (45.71%)<br>66  |  |  |
| Respiratory, thoracic and mediastinal<br>disorders                       |                         |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 6 / 70 (8.57%)<br>9     |  |  |

|                                                                                                                                                                                                                                                      |                                                                            |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--|--|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                         | 4 / 70 (5.71%)<br>7                                                        |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                               | 12 / 70 (17.14%)<br>43                                                     |  |  |
| Musculoskeletal and connective tissue disorders<br>Bone pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                                  | 52 / 70 (74.29%)<br>221<br><br>5 / 70 (7.14%)<br>7                         |  |  |
| Infections and infestations<br>Cystitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis<br>subjects affected / exposed<br>occurrences (all) | 5 / 70 (7.14%)<br>6<br><br>6 / 70 (8.57%)<br>12<br><br>5 / 70 (7.14%)<br>6 |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                         | 11 / 70 (15.71%)<br>17                                                     |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 01 April 2010     | <ul style="list-style-type: none"><li>- Allow intake of oral vinorelbine at home at Day 8, Day 15, and Day 22 of every cycle.</li><li>- Update to the name of the Clinical Pharmacy Responsible Person for the study.</li><li>- Prolongation of the patient enrolment period until Q2 2011.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 01 April 2010     | <ul style="list-style-type: none"><li>- Allow intake of oral vinorelbine at home at Day 8, Day 15, and Day 22 of every cycle.</li></ul> Information added to the master ICF <ul style="list-style-type: none"><li>- Modalities of dispensation of the study treatment at Day 1 of each cycle</li><li>- Modalities of storage of study treatment at the patient's home.</li><li>- Procedure for administration of Navelbine Oral (blood tests, agreement of the investigator before each intake at home)</li><li>- Completion of a patient diary</li><li>- Modalities of return of remaining capsules or empty blisters.</li></ul> - Improve the information given regarding the examinations to be followed by the patient and the person in charge of the study treatment at each study site. |
| 10 May 2010       | Update of the Investigator's list                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 22 February 2011  | <ul style="list-style-type: none"><li>- Allow inclusion of patients with unknown HER2 status.</li><li>- Prolongation of the patient enrolment period until 31-Mar-2012.</li><li>- Update the name of the Clinical Trial Coordinator and the address of the Clinical Pharmacy.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 17 October 2011   | Update of the Investigator's list                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 25 September 2013 | Update of the Investigator's list                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported