# EU Clinical Trials Register

## Clinical trial results:
## Randomised phase II study evaluating, as first-line chemotherapy, weekly oral vinorelbine as a single-agent versus weekly paclitaxel as a single-agent in oestrogen receptor positive, HER2 negative patients with advanced breast cancer.

### Summary

| | |
|---|---|
| EudraCT number | 2012-003530-16 |
| Trial protocol | AT ES PL FR |
| Global end of trial date | 05 September 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 November 2019 |
| First version publication date | 07 November 2019 |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | PM0259CA231B0 |

### 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, Boulgone-Billancourt, France, 92654 |
| Public contact | Gustavo Villanova, Pierre Fabre Medicament, +33 149 10 82 65, gustavo.villanova@pierre-fabre.com |
| Scientific contact | Gustavo Villanova, Pierre Fabre Medicament, +33 149 10 82 65, gustavo.villanova@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 | 18 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 December 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 September 2018 |
| Was the trial ended prematurely? | No |

Notes:


## General information about the trial

Main objective of the trial:

To evaluate, as a first-line chemotherapy, the disease control rate (DCR) of weekly oral vinorelbine as a single-agent versus weekly paclitaxel as a single-agent in oestrogen receptor positive, HER2 negative patients with advanced breast cancer.

Protection of trial subjects:

This study was performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

Background therapy:

Prophylactic oral anti-emetic medication with an 5-HT3 antagonist was recommended before each Oral Vinorelbine (OV) administration. In addition, the patient were to be provided with adequate oral antiemetics at home. Anti-emetic prophylaxis for patients receiving weekly paclitaxel was allowed and was given according to investigator's discretion. The use of corticosteroids as anti-emetic treatment was allowed. All patients were given premedication with corticosteroids, antihistamines, and H2 antagonists prior to paclitaxel therapy. Granulocyte stimulating growth factors may be given to patients who experienced febrile neutropenia, grade 4 asymptomatic neutropenia or neutropenic infection according to institutional rules.

Evidence for comparator:

The rationale for comparing Oral Vinorelbine (OV) and weekly Paclitaxel (PAC) as first-line chemotherapy for advanced ER-positive breast cancer patients is based on the fact that chemotherapy is widely used in the management of ER-positive breast cancer patients pre-treated by hormone therapy. The use of single-agent chemotherapy in this setting has been validated in guidelines of management of the disease. Both Paclitaxel and Vinorelbine are recommended among the standard available chemotherapy agents for Metastatic Breast Cancer (MBC).

| | |
|---|---|
| Actual start date of recruitment | 01 December 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Regulatory reason |
| Long term follow-up duration | 25 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:


## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Spain: 34 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Argentina: 8 |
| Country: Number of subjects enrolled | Brazil: 32 |

| | |
|---|---|
| Worldwide total number of subjects | 131 |
| EEA total number of subjects | 91 |

Notes:

## Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 82 |
| From 65 to 84 years | 48 |
| 85 years and over | 1 |

# Subject disposition

## Recruitment

Recruitment details:

Twenty-six active centres in 6 countries enrolled 131 oestrogen receptor positive, HER2 negative women with advanced breast cancer during a study inclusion period of 34 months.

## Pre-assignment

Screening details:

A 28-day screening period was planned before randomisation and screened for ER+/HER2- status women with advanced breast cancer. All screened patients were randomised 1:1 in the 2 arms.

## Period 1

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

Blinding implementation details:

This was an open-label study

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | OV arm |

Arm description:

66 patients were randomised in the OV arm.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Oral Vinorelbine (OV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

OV 60 mg/m²/week (day 1, 8, 15) for the first cycle, then increased to 80 mg/m²/week from the second cycle in the absence of severe haematological toxicity (one episode of grade 4 neutropenia or 2 consecutive episodes of grade 3 neutropenia during the initial treatment period). In case of severe haematological toxicity, the subsequent administrations were maintained at 60 mg/m²/week. Once increased to 80 mg/m²/week, in case of severe haematological toxicity the dose was reduced to 60 mg/m²/week with a possible re-escalation to 80 mg/m²/week if no haematological toxicity occurred during the last 3 administrations.

| **Arm title** | PAC arm |
|---|---|

Arm description:

65 patients were randomised in the PAC arm

| Arm type | Active comparator |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

weekly PAC, 80 mg/m²/week (day 1, 8 ,15), 1 hour infusion

| Number of subjects in period 1 | OV arm | PAC arm |
|---|---|---|
| Started | 66 | 65 |
| Completed | 2 | 0 |
| Not completed | 64 | 65 |
| Related adverse events | 3 | 11 |
| Other | 8 | 14 |
| Death | - | 2 |
| Non-related adverse events | 1 | 3 |
| Progressive disease | 52 | 35 |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | OV arm |
| Reporting group description: | |
| 66 patients were randomised in the OV arm. | |
| Reporting group title | PAC arm |
| Reporting group description: | |
| 65 patients were randomised in the PAC arm | |

| Reporting group values | OV arm | PAC arm | Total |
|---|---|---|---|
| Number of subjects | 66 | 65 | 131 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 42 | 40 | 82 |
| From 65-84 years | 24 | 24 | 48 |
| 85 years and over | 0 | 1 | 1 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.2 | 62.0 | |
| standard deviation | ± 10.6 | ± 11.0 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 66 | 65 | 131 |
| Male | 0 | 0 | 0 |
| Performance status reported in baseline clinical examination | | | |
| Units: Subjects | | | |
| 70 | 1 | 9 | 10 |
| 80 | 9 | 16 | 25 |
| 90 | 16 | 12 | 28 |
| 100 | 40 | 28 | 68 |
| Histopathological type | | | |
| Units: Subjects | | | |
| Ductal, nos | 39 | 35 | 74 |
| Invasive with predominant intraductal component | 12 | 11 | 23 |
| Lobular | 6 | 5 | 11 |
| Invasive, nos | 4 | 4 | 8 |
| Invasive | 1 | 3 | 4 |
| Intraductal | 1 | 1 | 2 |
| Other | 1 | 1 | 2 |
| Other ductal form | 0 | 2 | 2 |
| 30/40 | 1 | 0 | 1 |
| Cancer, nos | 0 | 1 | 1 |
| Inflammatory | 1 | 0 | 1 |
| Class K | 0 | 1 | 1 |
| Mucinous | 0 | 1 | 1 |
| TNM classification | | | |

| TNM classification at the time of first diagnosis | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Missing | 2 | 1 | 3 |
| Zero | 0 | 1 | 1 |
| One | 10 | 10 | 20 |
| 1C | 6 | 6 | 12 |
| Two | 26 | 32 | 58 |
| Three | 12 | 4 | 16 |
| Four | 4 | 9 | 13 |
| 4B | 2 | 2 | 4 |
| 4D | 1 | 0 | 1 |
| X Classification | 3 | 0 | 3 |
| Stage at diagnosis | | | |
| Units: Subjects | | | |
| IA | 7 | 12 | 19 |
| IB | 0 | 0 | 0 |
| IIA | 14 | 10 | 24 |
| IIB | 13 | 12 | 25 |
| IIIA | 12 | 11 | 23 |
| IIIB | 4 | 10 | 14 |
| IIIC | 4 | 5 | 9 |
| IV | 8 | 4 | 12 |
| UK | 4 | 1 | 5 |
| Histopathological grade | | | |
| Units: Subjects | | | |
| SBR I | 2 | 1 | 3 |
| SBR II | 22 | 27 | 49 |
| SBR III | 22 | 15 | 37 |
| Unknown | 20 | 22 | 42 |
| Primary tumour site | | | |
| Units: Subjects | | | |
| Bilateral | 4 | 3 | 7 |
| Left breast | 36 | 29 | 65 |
| Right breast | 26 | 33 | 59 |
| Oestrogen receptors status | | | |
| Units: Subjects | | | |
| Negative | 1 | 0 | 1 |
| Positive | 65 | 65 | 130 |
| Progesterone Receptors status | | | |
| Units: Subjects | | | |
| Negative | 14 | 7 | 21 |
| Positive | 52 | 58 | 110 |
| Body weight | | | |
| Units: kg | | | |
| arithmetic mean | 70.59 | 66.75 | |
| standard deviation | ± 15.45 | ± 12.95 | - |
| Body surface area | | | |
| Units: m^2 | | | |
| arithmetic mean | 1.71 | 1.67 | |
| standard deviation | ± 0.164 | ± 0.163 | - |
| Time between diagnosis and study entry | | | |

| Units: months | | | |
|---|---|---|---|
| arithmetic mean | 79.16 | 79.34 | |
| standard deviation | ± 58.84 | ± 64.61 | - |

## End points

### End points reporting groups

| Reporting group title | OV arm |
|---|---|
| Reporting group description: | |
| 66 patients were randomised in the OV arm. | |
| Reporting group title | PAC arm |
| Reporting group description: | |
| 65 patients were randomised in the PAC arm | |

### Primary: Disease control rate (DCR)

| End point title | Disease control rate (DCR) |
|---|---|

End point description:

Disease control rate (DCR) is defined as the number of patients with confirmed complete response (CR) + number of patients with confirmed partial response (PR) + number of patients with stable disease (SD) rates with a minimal duration of 6 weeks. Mean (SD) treatment duration was 27.31 (30.97) weeks for patients in the OV arm and 24.06 (20.97) weeks for patients in the PAC arm. Disease control was observed in 50 patients (75.8%; [95%CI: 63.6%; 85.5%]) in the OV arm (n=66) and 49 patients (75.4%; [95%CI: 63.1%; 85.2%]) in the PAC arm (n=65).

| End point type | Primary |
|---|---|

End point timeframe:

DCR according to investigator was calculated among the BOCR responders (CR and PR) and stable patients in the ITT population from the date of randomisation until the documentation of progression or death due to any cause.

| End point values | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: pourcentage | | | | |
| number (confidence interval 95%) | 75.8 (63.6 to 85.5) | 75.4 (63.1 to 85.2) | | |

### Statistical analyses

| Statistical analysis title | Primary efficacy analysis |
|---|---|
| Statistical analysis description: | |
| DCR was performed according to the Kaplan- Meier method. 95% CIs on the median were calculated using the Brookmeyer and Crowley method. | |
| Comparison groups | OV arm v PAC arm |

| Number of subjects included in analysis | 131 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | t-test, 2-sided |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 63.6 |
|     upper limit | 85.5 |

## Secondary: Objective Response Rate (ORR)

| End point title | Objective Response Rate (ORR) |
|---|---|

End point description:

Objective response rate (ORR) was defined as the sum of CR and PR rate and evaluated in the ITT population (n=131).

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

End point timeframe:

ORR was evaluated from the date of randomisation until the end of study treatment period in the ITT population (n=131).

| **End point values** | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: pourcentage | | | | |
| number (confidence interval 95%) | 19.7 (10.9 to 31.3) | 40.0 (28.0 to 52.9) | | |

## 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 duration of disease control (CR, PR and stabilisation of at least 6 weeks) was analysed in the subset of patients with disease control in the ITT population and estimated using Kaplan Meier anaylses. Patients who were lost to follow-up without progression, or reached the time point of analysis without a known record of progression or death had the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occurred last. Patients who received a new anti-tumoural treatment, whatever the type of treatment, before their disease progression were censored at the start date of that new anti-tumoural treatment.

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

End point timeframe:

Duration of disease control according to investigator was calculated among the BOCR stable patients from the date of randomisation until the documentation of progression or death due to any cause.

| End point values | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.8 (5.0 to 8.7) | 8.7 (7.0 to 10.0) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of stable disease

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

End point description:

Duration of SD (with best response SD ≥6 weeks or regardless the duration of best response SD) was analysed in a subset of patients with SD in the ITT population and estimated using the Kaplan Meier method. Patients who were lost to follow-up without progression, or reached the time point of analysis without a known record of progression or death had the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occurred last. Patients who received a new anti-tumoural treatment, whatever the type of treatment, before their disease progression were censored at the start date of that new anti-tumoural treatment.

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

End point timeframe:

Duration of stable disease (SD), according to investigator, was calculated among the stable patients from the date of randomisation until the documentation of progression or death due to any cause.

| End point values | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.6 (4.4 to 6.8) | 7.0 (3.3 to 8.7) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free survival (PFS)

| End point title | Progression-free survival (PFS) |
|---|---|

End point description:

PFS was estimated using the Kapaln Meier approach. Patients who were lost to follow-up, or reached the time point of analysis without a known record of progression or death 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. The mean duration of follow-up (SD) was 25.34 (14.69) months for the patients in the OV arm and 22.89 (14.81) months for patients in the PAC arm.

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

End point timeframe:

Progression-free survival (PFS) was calculated from the randomisation date until the date of first progression or date of death due to any cause if no progression was recorded before in the ITT population.

| End point values | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.5 (4.3 to 6.8) | 6.4 (5.1 to 8.3) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

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

End point description:

Overall Survival, defined as the duration between the date of randomisation and the date of death whatever the cause, was analysed in the ITT population. Overall survival of patients lost to follow-up before any record of death were censored at the date of last follow-up. Overall survival of patients alive at the time of analysis were censored at the date of last news (i.e. date of last administration, tumour assessment, clinical examination, haematological or biochemical assessment or date of last contact). At the cut-off date (18-Dec-2017) or last contact, death was reported for 96 patients (73.3%), 48 patients each in the two arms. Seventeen patients (25.8%) were still alive in the OV arm while 15 patients (23.1%) were still alive in the PAC arm. One patient (1.5%) in OV and two patients (3.1%) in PAC arm were lost to follow-up and two patients were still under treatment (both in OV arm).

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

End point timeframe:

Overall survival (OS) was analysed for the whole study period including follow-up. The median duration of follow-up (SD) was 25.34 (14.69) months for the patients in the OV arm and 22.89 (14.81) months for patients in the PAC arm.

| End point values | OV arm | PAC arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 | 65 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 27.6 (20.2 to 34.5) | 22.3 (13.5 to 27.6) | | |

### Statistical analyses

No statistical analyses for this end point

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

AEs were reported during the study treatment period. The mean duration of treatment (SD) was 27.31 weeks (30.97) for patients in the OV arm and 24.06 weeks (20.97) for patients in the PAC arm.

Adverse event reporting additional description:

At the cut-off date (18/12/17) or last contact, death was reported for 96 patients, 48 in each arm. 17 patients were still alive in the OV arm and 15 in the PAC arm. 1 patient in OV and 2 patients in PAC arm were lost to follow-up and two patients were under treatment (OV arm). The median RDI per cycle for OV was 72.7% and 94.0% for PAC.

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

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 16.0 |

## Reporting groups

| Reporting group title | Evaluable population for safety |
|---|---|

Reporting group description:

131 treated patients were evaluable for safety (patients who received at least one study treatment dose).

| Serious adverse events | Evaluable population for safety | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 131 (27.48%) | | |
| number of deaths (all causes) | 9 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon neoplasm | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |

| | | | | |
|---|---|---|---|---|
| **Lymphoedema** | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| **General disorders and administration site conditions** | | | | |
| asthenia | | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cough | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infiltration | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

**Investigations**

Activated partial thromboplastin time prolonged

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

**Injury, poisoning and procedural complications**

Femur fracture

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 131 (2.29%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Fall

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

**Cardiac disorders**

Acute coronary syndrome

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Cardiovascular insufficiency

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| 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 | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Granulocytopenia

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| 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 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

**Gastrointestinal disorders**

Vomiting

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 131 (2.29%) | | | |
| occurrences causally related to treatment / all | 3 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Abdominal pain

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Abdominal pain upper

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Ascites

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Constipation

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Gastric haemorrhage

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

**Musculoskeletal and connective tissue**

| | | | | |
|---|---|---|---|---|
| disorders | | | | |
| Pathological fracture | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rhabdomyolysis | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 4 / 131 (3.05%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopneumonia | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious pleural effusion | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

Frequency threshold for reporting non-serious adverse events: 4.6 %

| Non-serious adverse events | Evaluable population for safety | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 130 / 131 (99.24%) | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 41 / 131 (31.30%) | | |
| occurrences (all) | 202 | | |
| Weight increased | | | |
| subjects affected / exposed | 15 / 131 (11.45%) | | |
| occurrences (all) | 84 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 131 (8.40%) | | |
| occurrences (all) | 28 | | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 28 / 131 (21.37%) | | |
| occurrences (all) | 146 | | |
| Paresthesia | | | |
| subjects affected / exposed | 16 / 131 (12.21%) | | |
| occurrences (all) | 31 | | |
| Headache | | | |
| subjects affected / exposed | 13 / 131 (9.92%) | | |
| occurrences (all) | 28 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 62 / 131 (47.33%) | | |
| occurrences (all) | 219 | | |
| Peripheral oedema | | | |
| subjects affected / exposed | 20 / 131 (15.27%) | | |
| occurrences (all) | 59 | | |
| Pyrexia | | | |
| subjects affected / exposed | 19 / 131 (14.50%) | | |
| occurrences (all) | 25 | | |
| Asthenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 131 (12.98%) | | |
| occurrences (all) | 64 | | |
| **Chest pain** | | | |
| subjects affected / exposed | 10 / 131 (7.63%) | | |
| occurrences (all) | 31 | | |
| **Gastrointestinal disorders** | | | |
| Nausea | | | |
| subjects affected / exposed | 63 / 131 (48.09%) | | |
| occurrences (all) | 159 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 53 / 131 (40.46%) | | |
| occurrences (all) | 140 | | |
| Vomiting | | | |
| subjects affected / exposed | 48 / 131 (36.64%) | | |
| occurrences (all) | 103 | | |
| Constipation | | | |
| subjects affected / exposed | 25 / 131 (19.08%) | | |
| occurrences (all) | 36 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 16 / 131 (12.21%) | | |
| occurrences (all) | 36 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 131 (9.16%) | | |
| occurrences (all) | 22 | | |
| Stomatitis | | | |
| subjects affected / exposed | 11 / 131 (8.40%) | | |
| occurrences (all) | 13 | | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 23 / 131 (17.56%) | | |
| occurrences (all) | 60 | | |
| Cough | | | |
| subjects affected / exposed | 19 / 131 (14.50%) | | |
| occurrences (all) | 39 | | |
| **Skin and subcutaneous tissue disorders** | | | |

| | | | |
|---|---|---|---|
| Alopecia | | | |
| subjects affected / exposed | 32 / 131 (24.43%) | | |
| occurrences (all) | 207 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 23 / 131 (17.56%) | | |
| occurrences (all) | 59 | | |
| Back pain | | | |
| subjects affected / exposed | 18 / 131 (13.74%) | | |
| occurrences (all) | 36 | | |
| Pain in the extremity | | | |
| subjects affected / exposed | 16 / 131 (12.21%) | | |
| occurrences (all) | 41 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 21 / 131 (16.03%) | | |
| occurrences (all) | 40 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 05 November 2012 | Contraception duration after paclitaxel treatment |
| 16 July 2013 | Local Argentina<br>Pregnancy test frequency to local legislation |
| 04 October 2013 | Local Brazil<br>Only menopausal women or who underwent surgical sterilisation |
| 28 March 2014 | Extension inclusion period until December 2014 + Helsinki update + typo corrections + Navelbine investigator's brochure updates+ statistician |
| 20 October 2014 | Extension inclusion period until June 2015 |
| 29 October 2014 | Local Brazil<br>Pool of amendments PA05 and PA06 for unique submission to EC |
| 18 December 2017 | Change the definition of end of study |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

None reported