



## 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, Boulogne-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:

<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)	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
------------------------------	-----

<b>Arm title</b>	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/m<sup>2</sup>/week (day 1, 8, 15) for the first cycle, then increased to 80 mg/m<sup>2</sup>/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/m<sup>2</sup>/week. Once increased to 80 mg/m<sup>2</sup>/week, in case of severe haematological toxicity the dose was reduced to 60 mg/m<sup>2</sup>/week with a possible re-escalation to 80 mg/m<sup>2</sup>/week if no haematological toxicity occurred during the last 3 administrations.

<b>Arm title</b>	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/m<sup>2</sup>/week (day 1, 8, 15), 1 hour infusion

<b>Number of subjects in period 1</b>	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 analyses. 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  $\geq 6$  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 Kaplan 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



## 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 %

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

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 occurrences (all)	32 / 131 (24.43%) 207		
Musculoskeletal and connective tissue disorders			
Bone pain subjects affected / exposed occurrences (all)	23 / 131 (17.56%) 59		
Back pain subjects affected / exposed occurrences (all)	18 / 131 (13.74%) 36		
Pain in the extremity subjects affected / exposed occurrences (all)	16 / 131 (12.21%) 41		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	21 / 131 (16.03%) 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 Pregnancy test frequency to local legislation
04 October 2013	Local Brazil 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 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