



## 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
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#### 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
Public contact	Gustavo VILLANOVA M.D Oncology Medical Affairs Department, Pierre Fabre Médicament, +33 (0)149108265, gustavo.villanova@pierre-fabre.com
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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
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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
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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: 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: 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: 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: [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. 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
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical benefit rate

End point title	Clinical benefit rate
End point description: 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: 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)
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**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
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**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)			

<b>Attachments (see zip file)</b>	Kaplan-Meier Survival Time/Kaplan Meier Survival time.png
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**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of disease control**

End point title	Duration of disease control
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**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
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**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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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### Reporting groups

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



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