SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Navelbine Oral	**Referring to Module 5 of the Dossier**	
Name of active substance): Oral Vinorelbine	**Vol.: .....Page: .....**	

Title of study:	Randomized phase II study of the combination of oral vinorelbine (OV) with capecitabine (CAP) versus gemcitabine (GEM) in combination with paclitaxel (PAC) versus gemcitabine in combination with docetaxel (DOC) as first-line chemotherapy in patients with metastatic breast cancer. Study code: PM 0259 CA 223 B0	
Investigators:	35 principal investigators in 35 centres worldwide.	
Study centre(s):	35 centres in 14 countries	
Publication (references):	Final results of an international three-arm randomized phase II study evaluating oral vinorelbine plus capecitabine versus paclitaxel plus gemcitabine versus docetaxel plus gemcitabine as first-line chemotherapy in patients with metastatic breast cancer (NorCap-CA223 trial). S. Cinieri et al, presentation at ECCO 2013 (Amsterdam), Abstract 1905 S. Cinieri et al, presentation at ASCO 2014 (Chicago)	
Studied period: **(date of first enrolment)** **(date of last enrolment)**	 27/03/2007 28/12/2009	**Phase of development:** randomized phase II
Objectives: **Primary:** **Secondary:**	 Disease Control Rate (DCR) in the Intent to Treat (ITT) population Safety profile Response rate Disease Control Rate in the evaluable population Duration of Disease Control Duration of Stable Disease Duration of Response Progression free survival Time to treatment failure Overall survival Quality of life assessment	

Methodology:	Open label multinational randomized (1:1:1) phase II trial. Randomisation stratified according to minimization process and following factors: centre, prior adjuvant chemotherapy (anthracycline/ other) and age < or ≥ 65 years. **Treatment schedule** (Every 3-week cycles, until progressive disease, unacceptable toxicity or patient refusal) **Arm A: n=49*** Oral vinorelbine: 60 mg/m² on day 1 & day 8, for cycle 1, And then 80 mg/m² on day 1 & day 8**,** every 3 weeks for subsequent cycles**. Capecitabine : 1000 mg/m² twice a day (2000 mg/m² daily) from day 1 to day 14 **Arm B: n=50** Gemcitabine: 1250 mg/m² on day 1 & day 8 Paclitaxel: 175 mg/m² on day 1 **Arm C: n=50***** Gemcitabine: 1000 mg/m² on day 1 & 8 Docetaxel: 75 mg/m² on day 1 * 2 randomized patients have not been treated ** Dose increased from 60 to 80 mg/m² at cycle 2, in the absence of grade 3 or 4 toxicity in cycle 1 *** 1 randomized patient not treated
Number of patients (planned and analysed):	150 patients planned. 152 patients included. 149 patients treated and analysed.
Diagnosis and main criteria for inclusion:	**Inclusion criteria:** Women with: • Age ≥ 18 years, • Histologically confirmed adenocarcinoma of the breast; • Documented metastatic disease previously untreated by chemotherapy; • HER2 negative (assessed by 0-1+ IHC or 2+ IHC with FISH-) on the primary tumor or on metastatic site; • At least one measurable or non-measurable lesion using the RECIST criteria; • Women of childbearing potential must be using a medically accepted method of contraception (i.e. oral contraceptives, intrauterine devices) to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and for up to 3 months after the last dose of study treatment in such a manner that the risk of pregnancy is minimised; • Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the start of study treatment;

Diagnosis and main criteria for inclusion:

- Prior chemotherapy as follows:
  - adjuvant or neoadjuvant chemotherapy which may contain an anthracycline is allowed and relapsing more than 6 months after the end of chemotherapy;
  - patient previously treated with 5 FU infusion in adjuvant setting is allowed and relapsing more than 6 months after the end of chemotherapy.
- Prior hormonotherapy for neoadjuvant or metastatic breast cancer is allowed;
- Patients may have received prior radiotherapy but not on the sites used to assess response. A minimum of 4 weeks interval must have elapsed;
- Karnofsky Performance Status ≥ 70%;
- Life expectancy ≥ 16 weeks;
- Adequate bone marrow, hepatic and renal functions as evidenced by the following:
  - *Haemoglobin ≥ 10 g/dL;*
  - *Absolute Neutrophil Count ≥ 2 x 10^9/L;*
  - *Platelet Count ≥ 100 x 10^9/L;*
  - *Total Bilirubin < ULN (ULN: Upper Limit of Normal);*
  - *SGOT/SGPT ≤2.5 x ULN;*
  - *Alkaline phosphatase < 2.5 ULN (or < 5 ULN for bone metastases);*
  - *Creatinine Clearance > 50 mL/min; calculated using the Cockroft and Gault formula*;
- Absence of psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; these conditions should be assessed with the patient before registration in the trial;
- The patient must give written (personally signed and dated) informed consent before completing any study-related procedure.

Exclusion criteria:

- Local relapse alone after conservative treatment or contra-lateral tumor;
- Female is not eligible to enter the study if :
  - pregnant or lactating
  - with positive pregnancy test at inclusion;
- Female of childbearing potential who is unwilling or unable to use a medically accepted method to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and at least 3 months following the last dose of study treatment;
- Patients with symptoms suggesting CNS involvement or leptomeningeal metastases;
- Concomitant hormonal therapy for metastatic breast cancer;

	• Malabsorption syndrome or disease significantly affecting gastro-intestinal function or major resection of the stomach or proximal small bowel that could affect absorption of capecitabine and oral vinorelbine (Navelbine Oral®); • Prior severe and unexpected reaction to fluoropyrimidine therapy (with or without documented DPD deficiency) or known hypersensitivity to 5-fluorouracil, or patient with a history of hypersensitivity reactions to product containing cremaphor®; • Prior chemotherapy in the metastatic setting; • Patients previously treated with a vinca-alkaloid, capecitabine, gemcitabine or taxanes; • Current peripheral neuropathy ≥ grade 2 according to NCI criteria; • Patients with dysphagia, or inability to swallow the tablets; • Other serious illness or medical conditions: © Cardiac disease; © Unstable diabetes; © Uncontrolled hypercalcemia; © Clinically significant active infections; © Previous organ allograft; • Requirement for concurrent use of the antiviral agent (sorivudine) or chemically related analogues such a brivudine; • Participation in another clinical trial with any investigational drug within 30 days prior to registration; • History of another malignancy within the past five years except basal cell carcinoma of the skin or carcinoma in situ of the cervix.
Test product	ORAL VINORELBINE
Mode of administration	ORAL
Doses	60 mg/m^2 day 1 + day 8 (cycle 1); 80 mg/m^2 day 1 + day 8 for subsequent cycles in the absence of grade 3-4 toxicity at cycle 1 (every 3 weeks)
Batch numbers	NAVELBINE Oral 20 mg: AQ20122 - AQ20139 - AQ20146 - AQ20157 - AQ20194 NAVELBINE Oral 30 mg: AQ30125 - AQ30138 - AQ30147 - AQ30160 - AQ30192 - AQ30196
Other products **Modes of administration**	CAPECITABINE (oral), GEMCITABINE, PACLITAXEL, DOCETAXEL (intravenous). - Dosing: capecitabine 1000 mg/m^2 twice a day (2000 mg/ m^2 daily) from day 1 to day 14, every 3 weeks - Dosing gemcitabine: 1250 mg/m² on day 1 & day 8 (in combination with paclitaxel), 1000 mg/m² on day 1 & day 8 (in combination with docetaxel), every 3 weeks

	- Dosing paclitaxel: 175 mg/m^2 on day 1 every 3 weeks - Dosing docetaxel: 75 mg/m^2 on day 1 every 3 weeks Commercial products
Duration of treatment:	Patients showing an objective response complete response (CR) or partial response (PR) or stable disease continued treatment until progressive disease, unacceptable toxicity or patient refusal.
Criteria for evaluation: **Efficacy:**	**Efficacy Measures**: The primary efficacy analysis was to evaluate the Disease Control Rate (DCR) according to RECIST criteria (version 1.1) [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) rates] in each arm on the intent to treat population, the 95% confidence interval being provided. Assessment interval: tumour assessment (measurable and non-measurable lesions) was performed at baseline and every 6 weeks; tumour response and progression (PD) was assessed for all randomized patients by the investigators. Secondary efficacy endpoints included the following: Disease Control Rate on the evaluable population, Response Rate (both best overall response and objective confirmed response), duration of Disease Control, duration of stable disease, duration of response, time to first response, Time to Treatment Failure (TTF), Progression Free Survival (PFS), Overall Survival (OS), Duration of disease control and response were evaluated for all patients with disease control and responding patients, respectively.
Safety:	**Safety Measures**: physical examination and vital signs, performance status, complete blood cell counts, serum chemistry, clinical safety, adverse events using the NCI Common Toxicity Criteria (version 2.0).
Statistical methods:	Study Primary Objective and Statistical Methodology - Primary objective: To evaluate the Disease Control Rate of oral vinorelbine in combination with capecitabine (OV + CAP) , gemcitabine in combination with paclitaxel (GEM + PAC) and gemcitabine in combination with docetaxel (GEM + DOC) in HER2-negative metastatic breast cancer patients. Disease Control Rate was defined as the sum of the complete, partial responses and stable disease rate. For patients with stable disease, a minimal duration of 3 months was required. - Statistical methodology: the reference disease control rates, acceptable error probabilities, and number of testings selected for this study were as follows for each arm: $p_0 = 0.50$ $p_A = 0.75$ $\alpha \leq 0.05$ $\beta \leq 0.20$ $k = 2$ This assumed that 50 % was the minimum desirable disease control rate for an active regimen in this population. Under these conditions, the total sample size (N) was of 45 evaluable patients in each treatment arm. Patients were stratified according to center, prior anthracycline in the (neo)adjuvant setting and age < or ≥ 65 years.

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Patients characteristics

	OV + CAP n=49	GEM +PAC n=50	GEM + DOC n=50
Median Age in years (range)	58 (33-76)	56 (29-78)	57 (33-77)
<65 years	82%	80%	76%
≥65 years	18%	20%	24%
Median Karnofsky PS	90	90	90
Hormone receptor positive	61%	50%	66%
Prior (neo)adjuvant chemotherapy	47%	44%	54%
Prior anthracycline	39%	42%	42%
Prior hormone therapy (adjuvant + advanced settings)	59%	64%	66%
Prior hormone therapy for advanced disease	22%	30%	40%
Measurable disease at baseline	94%	90%	98%
Visceral involvement	80%	82%	74%
Liver metastases	49%	52%	48%
Lung metastases	47%	50%	40%
Bone metastases	55%	66%	72%
Number of metastatic sites:			
- **1**	18%	6%	8%
- **2**	29%	50%	34%
- **≥3**	53%	44%	58%

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Treatment administration and drug exposure

	OV + CAP n=49	GEM + PAC n=50	GEM + DOC n=50
Median duration of treatment in weeks (range)	19 (3-115)	19 (3-40)	21 (3-78)
Median number of cycles (range)	6 (1-37)	6 (1-12)	7 (1-25)
Patients receiving at least 6 cycles	61%	78%	72%
Patients receiving more than 6 cycles	41%	36%	52%
Patients receiving at least 18 cycles	10%	0%	4%
Median Relative Dose intensity	OV: 81% CAP: 79%	GEM: 84% PAC: 95%	GEM: 58% DOC: 90%
OV: Dose escalation to 80 mg/m² at cycle 2	78%		

Efficacy results

ITT population	OV + CAP n=49	GEM + PAC n=50	GEM + DOC n=50
CR / PR (RECIST)	2% / 31%	0/ 24%	2% / 48%
Objective response rate - CR + PR - [95% CI]	33% [20-48]	24% [13-38]	50% [36-64]
Disease Control Rate (CR+PR+SD ≥ 3 months) [95% CI]	73.5% [59-85]	78% [64-88]	80% [66-90]

Median duration of Disease Control [95% CI]	8.1 months [6.1-25.8]	8.0 months [6.0-9.0]	13.1 months [9.9-25.4]
Progression-Free Survival [95% CI]	7.6 months [6.0-11.0]	9.0 months [7.0-11.2]	11.4 months [7.6-13.8]
Time to Treatment Failure [95% CI]	4.6 months [3.2-6.0]	4.8 months [4.6-5.6]	5.2 months [4.4-6.8]
Overall Survival [95% CI]	30.2 months [24.0-42.2]	29.6 months [21.2-42.2]	31.0 months [24.2-40.0]

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Safety results

Worst Haematological Safety Grade 3/4 NCI CTC v2 per patient

	OV + CAP n=48*			GEM + PAC n=50			GEM + DOC n=50		
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Anemia	0	2%	2%	4%	0	4%	8%	0	8%
Neutropenia	25%	25%	50%	36%	10%	46%	30%	56%	86%
Thrombocytopenia	0	0	0	0	0	0	2%	4%	6%
Febrile Neutropenia	4 patients**			0***			3 patients		

*1 patient not evaluable for haematological toxicity

** plus 2 toxic deaths in Arm A due to neutropenic infection

*** 1 toxic death due to septic shock

Worst Non-Haematological Safety Grade 3/4 NCI CTC v2 per patient

	OV + CAP n=49		GEM + PAC n=50		GEM + DOC n=50	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	8%	0	4%	0	2%	0
Vomiting	10%	0	2%	0	2%	0
Diarrhoea	6%	0	4%	0	2%	0
Constipation	2%	0	0	0	0	0
Abdominal Pain	4%	0	0	0	0	0
Stomatitis	2%	0	0	0	2%	0
Hand-foot syndrome	8%	0	0	0	0	0
Fatigue	10%	0	10%	2%	22%	0
Documented Infection	2%	0	2%	0	10%	0
	Grade 2		Grade 2		Grade 2	
Alopecia	8%		72%		76%	

Conclusion	• The DCR as well the OS results reported in this trial confirm that the full oral combination of OV + CAP is an active combination which can be proposed as an alternative to taxane-based regimens as first-line CT in MBC, allowing to delay the constraints of an intravenous CT. • As expected, each regimen presented a specific and particular tolerance profile, with a very low incidence of alopecia after full oral CT.