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L00070 IN 311 B0

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L0070 I.V. Vinflunine

Clinical study protocol

A multicentre, randomised, phase III study of vinflunine plus capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with an anthracycline and a taxane

Pierre Fabre Study Code: L00070 IN 311 B0

Sponsor's representatives:

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STUDY SYNOPSIS

Name of SPONSOR: **Pierre Fabre MEDICAMENT**		
Name of finished product:	JAVLOR®	
Name of active substance(s):	VINFLUNINE DITARTRATE	

Title of the study

A multicenter, randomised, phase III study of vinflunine plus capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with an anthracycline and a taxane (L00070 IN 311 B0).

Coordinating investigators: Binghe Xu

Planned number of study centres:

26 centres have been active in China, Singapore and Taiwan.

Study rationale

Options for the treatment of patients who have progressed after an anthracycline and a taxane are limited. Capecitabine currently has a role in this setting, yet as many as 80% of patients do not respond to this treatment and those who respond eventually develop clinical resistance.

The antitumour activity of vinflunine has been demonstrated in patients with breast cancer after exposure to anthracycline and to taxane.

Vinflunine plus capecitabine has been shown to be a feasible combination for patients previously treated with an anthracycline and a taxane. Each drug in combination can be administered at efficacious doses.

This population has few therapeutic options with established clinical benefit. The development of a new regimen and potential new standard of care for this group is important.

Period of inclusion Q3 2013 to Q4 2014	**Clinical phase Phase III**

Objectives

- Primary objective:

- To compare in patients with advanced breast cancer pretreated with anthracycline and taxane the efficacy of the combination of vinflunine and capecitabine with capecitabine alone, in terms of progression-free survival.

- Secondary objectives:

The secondary objectives listed below will be no more evaluated:

- To evaluate the response rate, the time to response and the duration of response in both arms
- To compare the disease control rate between arms
- To evaluate the duration of disease control in both arms
- To evaluate the overall survival in both arms

Except following secondary objective, which will be evaluated:

- To evaluate safety

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Methodology

This multicentre, open-label, randomised, Phase III study planned to enrol a total of 334 patients. The sponsor decided to stop the recruitment after enrolment of a total of 112 patients with advanced breast cancer who have previously been treated with an anthracycline and a taxane. Patients will be randomised in a 1:1 ratio to receive VFL plus capecitabine (Arm A) or capecitabine alone (Arm B).

Randomisation will be stratified according to :

1. Karnofsky Performance Status ("90-100%" versus "70-80%"),
2. Visceral involvement (yes versus no), visceral lesions include one of the following : liver, lung, pleura (including pleural effusion), heart (including pericardial effusion), peritoneum (including abdominal ascites), spleen and adrenal glands,
3. Investigator site.

Number of patients

A sample size of 167 patients per arm was planned. Following the sponsor decision, a total of 112 patients have been enrolled in this. The inclusions are now closed.

Diagnosis and main inclusion criteria

Inclusion criteria :

1. Patients must give written informed consent
2. Women with histologically or cytologically confirmed Her-2 negative carcinoma of the breast.
3. Documented locally recurrent or metastatic disease not amenable to curative surgery or radiotherapy.
4. Patients must have received either one, two or three prior chemotherapy regimens including those administered in the neoadjuvant or adjuvant setting (neoadjuvant chemotherapy followed by adjuvant chemotherapy will count for one line).
5. Prior treatment must have included both an anthracycline (i.e., doxorubicin or pirarubicin or epirubicin) and a taxane (i.e., paclitaxel or docetaxel) in any combination or order whatever the setting.
   Note that the patients must have received a minimum cumulative dose of 180 mg/m² of doxorubicin/ pirarubicin or 300 mg/m² of epirubicin.
6. Documented progression on or within 12 months of the most recent chemotherapy.
7. Prior hormone therapy is allowed either in the neoadjuvant and/or adjuvant setting and in the advanced setting provided that the treatment is terminated 2 weeks prior to randomisation.
8. Prior radiation therapy is allowed to < 30% of the bone marrow and must be completed at least 3 weeks before randomisation.
9. Must have measurable or non measurable disease according to RECIST (version 1.1). In patients who present with a single lesion, available histological or cytological confirmation is required.
10. Adequate recovery from recent surgery. At least one week must have elapsed from the time of minor surgery, at least 3 weeks for major surgery.
11. Estimated life expectancy ≥ 12 weeks.
12. Karnofsky performance score ≥ 70%.
13. Age ≥ 21 years and < 80 years.
14. Adequate haematological function defined by absolute neutrophil count > 1.5 x 109/L, platelet count > 100 x 109/L and haemoglobin > 10 g/dL.

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15. Adequate hepatic function defined by total bilirubin < 1.5 x upper limit of normal (ULN) ; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x ULN (or < 5 x ULN in case of liver metastases) ; alkaline phosphatase < 5 x ULN
16. Adequate renal function defined as calculated creatinine clearance > 50 ml/min according to Cockroft-Gault formula
17. ECG without clinically relevant abnormality
18. Patients on coumadin or warfarin must be on stable doses and have an International Normalized Ratio (INR) ≤ 3 at the time of screening.
19. Women of childbearing potential must be using a medically accepted method of contraception (i.e. intrauterine devices, condom) 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 first treatment administration.
20. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial.

Exclusion criteria :

1. Patients with known or with clinical evidence of brain metastasis or leptomeningeal involvement
2. Patients with pulmonary lymphangitis or symptomatic pleural effusion (grade ≥ 2) that results in pulmonary dysfunction requiring active treatment.
3. Patients having received any other experimental drug or chemotherapy within 30 days before randomisation.
4. History of second primary malignancy, except: bilateral breast carcinoma, in situ carcinoma of the cervix, adequately treated non melanomatous carcinoma of the skin, and other malignancy treated at least 5 years previously with no evidence of recurrence.
5. Patients with pre-existing motor/sensory peripheral neuropathy of NCI CTCAE version 3.0 grade > 1.
6. Patients having received > 3 regimens of chemotherapy
7. Prior therapy with capecitabine and/or vinca alkaloids (including vinflunine)
8. History of severe hypersensitivity to vinca alkaloids and/or to fluoropyrimidine or any contra indication to any of the study drugs.
9. Known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency.
10. A female is not eligible to enter the study if: pregnant or lactating or with positive pregnancy test at inclusion.
11. 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.
12. Known history of HIV infection.
13. Inability to take and/or absorb oral medication including previous gastric surgery or any evidence of partial oesophageal, gastric, small or large bowel obstruction; gastrointestinal disorder that affect the absorption of capecitabine (malabsorption syndrome, 2/3 gastric resection and bowel resection).
14. Patients who have any serious, concurrent uncontrolled medical disorder especially uncontrolled hypercalcaemia, congestive heart failure, uncontrolled high-risk hypertension, arrhythmia, angina pectoris or previous history of myocardial infarction within 6 months prior to randomisation
15. Prior bone marrow transplantation or autologous stem cell infusion following high-dose chemotherapy..

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Test product, dose and mode of administration

Patients randomised in arm A will receive:

Vinflunine at the dose of 280 mg/m² on day 1 of each cycle every 3 weeks, over a 20-minute IV infusion.

In addition, patients will receive capecitabine which will be self administered in the outpatient setting. Patients will take 825 mg/m² twice daily orally for 14 consecutive days beginning on day 1 of each cycle followed by 1 week of rest.

A cycle of therapy is defined as 3 weeks.

Reference therapy, dose and mode of administration

Patients randomised in arm B will receive:

Capecitabine self administered in the outpatient setting. Patients will take 1250 mg/m² twice daily orally for 14 consecutive days beginning on day 1 of each cycle followed by 1 week of rest. A cycle of therapy is defined as 3 weeks.

Duration of treatment

Patients will continue the study treatment until :

- disease progression,
- unacceptable toxicity
- patient's request

Criteria for evaluation:

- Efficacy assessment

Efficacy will be determined by using RECIST (version 1.1). All lesions will be assessed at baseline then every 6 weeks (+/- 3 working days) from randomisation (regardless of the timing of treatment cycles).

- Safety assessment

Clinical safety will be assessed by:

- complete history of malignant and non malignant disease.
- full physical examination including vital signs, weight, PS, and neurological examination
- ECG at baseline and at the end of treatment
- regular reporting of adverse events that will be graded by using NCI CTCAE version 3.0
- complete blood count at baseline then on day 1 of each cycle
- serum chemistry at baseline then on day 1 of each cycle.

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Statistical methods

As the final population size is much lower than the population size required to ensure adequate statistical power, , the collection of data will be stopped and the analyses will be performed when patients have either completed the end of treatment period or completed 35 cycles. As patients are not followed until progression, the results should be not representative and they will only be used as exploratory data.

The primary objective of this study is to show the superiority of the vinflunine plus capecitabine combination (arm A) versus capecitabine alone (arm B) in terms of progression-free survival in breast cancer patients after anthracycline and taxane failure.

It is assumed that the median progression-free survival will be 4.0 months for the control arm (arm B). The goal of the study is to show a PFS improvement of 1.5 months (HR=0.727) i.e. a median PFS of 5.5 months for the VFL plus capecitabine arm.

Using a two sided log-rank test with a target type I error $\alpha = 5\%$, it is required to observe 310 events (progression or death) in order to have a 80% power $(1 - \beta)$ to show a statistically significant PFS difference when the true hazard ratio is 0.727.

An approximately 24 months accrual period was planned for the 334 patients. Following the decision to stop the recruitment, the statistical analysis will be actually conducted on the 112 randomised patients **and only descriptive analyses will be performed on the ITT population**.

The primary efficacy analysis will be **the description of median PFS in the ITT population.**.

The safety analysis will be performed in the evaluable population for safety. Haematological parameters (WBC, ANC, platelets, haemoglobin), febrile neutropenia, biochemical parameters (ALT, AST, alkaline phosphatase, creatinine, total bilirubin) and non haematological toxicities will be assessed. The NCI CTCAE version 3.0 will be used except hand-foot-syndrome which will be graded using Roche Hand-Foot-Syndrome Grading Scale.

End of study

The end of study is **the date of the last patient study treatment administration plus 30 days (EOT).**

No follow up period assessments will be performed subsequently to the approval of the amendment PA06:

-Patients under treatment will stop the study at End Of Treatment (EOT)

-Patients under follow up will stop the study immediately.

Table 1: Study flow chart

Required assessments	Screening period	Treatment period			End of Treatment (d)	Follow-Up (f)
Timing	**Day -21 to -1**	**Day 1 every cycle**	**Day 1 to Day 14**	**Every 6 weeks**		
Signed Informed Consent	X (a)					
Study treatment						
Vinflunine (Arm A)		X				
Capecitabine (Arms A + B)			X			
Demographic data						
Demography/Medical History/Diagnosis and prior therapy	X					
Her-2 status and ER/PgR status	X (q)					
Serum/urine pregnancy test in women of childbearing potential	X (j)					
Physical Examination/Vital signs/Weight Neurological examination	X (b)	X			X	
Karnofsky Performance Status	X (b)	X			X	
Safety						
Electrocardiogram (ECG)	X (b)	X (o)			X	
Pretreatment events / Adverse events/ SAE	X (k)	X			X	X
Complete blood count	X (b)	X (n)			X	
Blood chemistry (c)	X (b)	X (p)			X	
INR (as clinically indicated) (l)	X					
Concomitant medications/blood Products	X (k)	X			X	
Efficacy (i)						
Chest CT-Scan or MRI	X			X	X (g)	
Abdominal/pelvic CT-scan or MRI	X			X	X (g)	
Bone scintigraphy (e)	X				X (g)	
Bone X-rays or CT scan (bone window) or MRI (h)	X			X (h)	X (g)	
Clinical/biological skeletal parameters/related events (m)	X	X			X (g)	
Brain CT scan or MRI if clinical suspicion of CNS metastases	X					
Other imaging if necessary	X			X	X (g)	

(a): Prior to any study procedure.
(b): Within 7 days prior to first study drug treatment.
(c): Transaminases, alkaline phosphatases, total bilirubin, total protein, urea, creatinine and calculated creatinine clearance, calcium, sodium and potassium.
(d): 30 days ± 3 days after study treatment discontinuation.
(e): Bone scintigraphy in all patients at baseline. To be repeated in the following cases:
- In patients who had bone lesions at study entry to document an overall complete response
- In all patients: at any time during study treatment in case of suspicion of progression due to skeletal related events defined as any observation of the following clinical/biological parameters: increase in pain intensity or analgesic consumption or alkaline phosphatase level or calcium level; or new bone pain symptoms requiring other palliation therapy i.e. radiotherapy, surgery, bisphosphonates; or spinal cord compression; or pathological bone fracture.

(f): Only for patients who discontinued study participation before approval of PA06 :until disease progression: every 6 weeks. After disease progression, every 6 months until death or end of study.
(g) Only for patients who discontinued study participation before approval of PA06 ::in case of treatment discontinuation for other reason than PD, all efficacy assessments including clinical and biological parameters of bone lesion (described above) must be performed every 6 weeks until disease progression is documented, then survival information will be collected approximately every 6 months until death or end of study. Bone scintigraphy should be performed at any time in case of worsening of at least one of the clinical/biological parameters described above.
(h): If deemed necessary by the investigator ; to be performed on hot spots of bone scintigraphy
(i): Tumour assessment is to be performed every 6 weeks (+/- 3 working days) from randomisation (regardless of the timing of treatment cycles): all lesions found at baseline should be re-investigated at each tumour assessment (for bone lesions, see specific assessment guidelines in Section 8.1.1.2). Additional examinations may be performed if appearance of new lesions is suspected.
(j): Within 72 hours prior to first study drug treatment
(k) Within 2 weeks prior to first study drug treatment
(l) Patients on oral coumarin derivative should have their anticoagulant response (INR) monitored closely
(m) Including evaluation of bone pain, analgesic consumption and assessment of biological parameters (alkaline phosphatases, calcaemia)
(n) to be performed within 24 hours before day 1 of each cycle
(o) if clinically indicated
(p) same than (n) except at cycle 1 day 1
(q) to be known prior to randomisation