2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Vinflunine	**Referring to Module 5 of the Dossier**	
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Title of study: Phase III study of vinflunine plus gemcitabine versus paclitaxel plus gemcitabine in patients with unresectable, locally recurrent or metastatic breast cancer after prior anthracycline-based adjuvant chemotherapy (L00070 IN 303 B0)

Coordinating Investigators: Antonio LLOMBART, MD, Study Chairman, Spain; Henri ROCHE, MD, France; Robert PARIDAENS, MD, Belgium; Armando SANTORO, MD, Italy; Denis TALBOT, MD, United Kingdom.

Study centres: 163 centres in 19 countries participated in this study.

Publication (reference): None

Study period: **Date of first patient enrolled:** 27th June 2006 **Last patient last visit:** Ongoing **Study cut-off date:** 30th June 2011	**Phase of development:** III

Objectives:

Primary: To show that the vinflunine plus gemcitabine test arm is non inferior to the paclitaxel plus gemcitabine control arm in terms of progression-free survival.

Secondary: To compare between the 2 treatment arms:

- the tumour response rate,
- the duration of response, duration of disease control, time to treatment failure and time to first response,
- the overall survival,
- the safety profile,
- the health-related quality of life through the EORTC questionnaire.

Methodology: Open-label, multicentre, randomised, phase III trial. Randomisation was stratified according to a minimisation process on the following factors:

- Investigational centre
- Karnofsky Performance status ("90-100" versus "70-80")
- Previous taxanes ("yes" versus "no")
- "Measurable disease" versus "non measurable disease"
- Visceral lesions ("yes" versus "no"). Visceral lesions included at least one of the following: liver, lung, pleura, heart, peritoneum, spleen and suprarenal glands.

Number of patients (planned and analysed):

A total of 904 patients had to be enrolled in this phase III study. To accommodate an anticipated 10% loss of patients to follow-up, 994 patients in total had to be randomised.

A total of 1004 patients were enrolled:

- Arm A – vinflunine plus gemcitabine : 503 randomised patients
- Arm B – paclitaxel plus gemcitabine : 501 randomised patients

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Diagnosis and main criteria for inclusion:

Inclusion criteria:

- Patients had to give written informed consent (personally signed and dated) before completing any study-related procedure which meant assessment or evaluation that would not form part of the normal medical care of the patient.
- Women with histologically or cytologically confirmed carcinoma of the breast.
- Documented locally recurrent or metastatic disease not amenable to curative surgery or radiotherapy.
- Patients with either:
- HER-2 negative disease assessed by IHC 0-1+ or FISH/CISH negative, on the primary tumour or metastatic site.
- HER-2 status unknown provided that a tumour sample was available for retrospective review, if relevant.
- Patients had to have received a prior neoadjuvant and/or adjuvant anthracycline-based chemotherapy (or, if contraindicated, a non-anthracycline based chemotherapy) with or without a taxane. The disease free interval from completion of the prior chemotherapy had to be more than 12 months.
- Prior hormone therapy was allowed both in the neoadjuvant and/or adjuvant setting and in the metastatic setting provided that there had been documented progression of the disease and the treatment had been terminated prior to randomisation.
- Prior radiation therapy was allowed to < 25% of the bone marrow and had to be completed at least 4 weeks before randomisation.
- Patients with measurable or non-measurable lesions using the RECIST guidelines.
- Estimated life expectancy ≥ 12 weeks.
- Karnofsky performance score ≥ 70%.
- Age ≥ 18 and ≤ 75 years old.
- Adequate haematological function as defined by absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and haemoglobin ≥ 10 g/dL (within 7 days before first study treatment).
- Adequate hepatic function as defined by: total bilirubin ≤ 1.5 x upper limit of normal (ULN), AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN in case of liver metastases, alkaline phosphatase ≤ 5 x ULN (within 7 days before first study treatment).
- Adequate renal function as defined by: creatinine level within normal values or, in case of creatinine level > ULN, calculated creatinine clearance ≥ 60 mL/min according to Cockroft-Gault formula (within 7 days before first study treatment).
- ECG without clinically relevant abnormality (within 7 days before first study treatment).
- Women of childbearing potential had to use a medically accepted method of contraception (i.e. oral contraceptives, 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. Women of childbearing potential had to have a negative serum or urine pregnancy test within 72 hours prior to first study treatment administration.

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Exclusion Criteria:

- Patients who had received previous chemotherapy for metastatic disease or progressed while on adjuvant chemotherapy or within 12 months from completion of adjuvant chemotherapy.
- Patients with known or with clinical evidence of brain metastases or leptomeningeal involvement.
- Inflammatory breast cancer without evidence of metastatic disease.
- Patients who had received any other experimental or anti-cancer therapy within 30 days before randomisation except hormone therapy.
- History of second primary malignancy, except: bilateral breast carcinoma, in situ carcinoma of the cervix, adequately treated non melanomatous carcinoma of the skin, or other malignancy treated at least 5 years previously with no evidence of recurrence.
- Patients having as the sole tumour lesion, any of the following: malignant effusion, lymphangitis, cystic lesion, bone lesion; and any other lesion that was not assessed by imaging techniques or colour photography.
- Patients with pre-existing motor/sensory peripheral neuropathy of CTCAE version 3.0 grade > 1.
- Prior therapy with gemcitabine and/or Vinca alkaloids.
- History of severe hypersensitivity to Vinca alkaloids and/or gemcitabine and/or taxanes or any contraindication to any of the study drugs.
- Pregnant or breast feeding women.
- Patients who had 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.
- Prior bone marrow transplantation or autologous stem cell infusion following high-dose chemotherapy.
- Patients with psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; and patients under guardianship (e.g. individuals who were not able to freely give their informed consent). These conditions should have been assessed with the patient before randomisation.

Test product, Dose, Mode of administration, Batch number:

Arm A (test arm):

Patients in arm A received: Vinflunine (VFL) at the dose of 320 mg/m² on day 1 as a 20-minute i.v. infusion followed by gemcitabine (GEM) at the dose of 1000 mg/m² on day 1 as a 30-minute i.v. infusion every 3 weeks. On day 8, gemcitabine (1000 mg/m²) was administered as a 30-minute i.v. infusion.

Anti-emetic prophylaxis: corticosteroids (dexamethasone 8 mg PO or methylprednisolone 64 mg PO) daily from day 1 to day 3, in combination with a serotonin antagonist on day 1.

Constipation prophylaxis: laxatives and dietary measures starting from the day before each vinflunine administration to day 5 or 7.

Doses modifications for both study drugs according to haematological and non-haematological toxicities were predetermined in the study protocol.

In the initial protocol, patients who did not experience any haematological or non-haematological toxicity requiring dose reduction during the first cycle underwent an increase of gemcitabine dose at cycle 2 to 1250 mg/m² on days 1, 8 of three-week cycles. As planned by the protocol, an interim safety analysis was performed on the first 61 evaluable patients treated in arm A. Following the Independent Data Monitoring Committee (IDMC) review meeting held on 12th October, 2007, it was decided to stop the intra-patient dose escalation of gemcitabine in arm A. The termination of the dose escalation was effective as of 29th October, 2007.

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Batch numbers:

- Vinflunine: 250 mg: 10P001, SB0263, SB0475/B, SB0476, SB0579/A, SB0579/B
- Vinflunine: 50 mg: SB0306, SB0639.

Reference Therapy, Dose, Mode of administration, Batch number:

Arm B (control arm):

Patients in arm B received: Paclitaxel (PTX) at the dose of 175 mg/m² on day 1 over approximately 3 hours as an i.v. infusion, followed by gemcitabine at the dose of 1250 mg/m² as a 30-minute i.v. infusion every 3 weeks. On day 8, gemcitabine (1250 mg/m²) was administered as a 30-minute i.v. infusion.

Anti-emetic prophylaxis and pre-medication to prevent hypersensitivity reactions were used according to institutional guidelines.

In case of occurrence of any toxicity requiring dose reduction (see definition above): the dose of both drugs was to be reduced.

However, in case of occurrence of any paclitaxel-induced peripheral neuropathy, only the PTX dose had to be reduced.

Batch numbers:

- Taxol 300 mg: 6E17523, 6B18157, 6M12114, 8A34789, 8K36103, 9F47562, 9K47733, 8A34782, 0A58794, 9L51882, 0D55103, 6L19450, A-001, 0D55103C, OF56810, 6H17013, 6K18087, 6L18741, 6M09470, 7A27897, Z-002, 7F25933, 8K40390, 9A48101, 9A56108
- Taxol 100 mg: 6C11563, 6L19450, 8H29674, 8A34922, 0A58791, 0D56106, 0D56016, 8M29674, 9C47969, 9J54524, 8C39161, 09D15LA, 08J01NB, A-003, A-002
- Generic paclitaxel 300 mg: 09AL19TD, 09B16NC, 09E25LA, 7016847AG, T056847AC, 0GA19TD, 3036869AA, 713441, 706485, 709857, 710565, 713153, 09E28LA, W036872A, X016872AA, 07B14LA, 07G24KA, 06106LD, SO26872AA, 92478303, 92581804, 92711803, 93086405, 93459704, 100518025, 100223007, 100316026, 100406008, 100427004, 07B141A, 07G07MA, 07G27HA, 07G27MA, 083210A, 08G14QA, 08J210A, 804809
- Generic paclitaxel 100 mg: 7036844AI, 7036844AI, SO16868, 07C190F, 07H150C, 709859, 6B072B, 06E18MB, 07C190E, 09F18PC 06F01NA, 08F19PA, 06D130A, 07G23KA, 709570, 710810, 713150, 801682, T026866AA, 21DA03PA/1, 09A14LB, PA09P018T1, PA09K011T1, PA09P01811
- Generic paclitaxel 30 mg: 702358, 705141, 706484, 07B08LB, 07D170N, 08L02OB, 08A25K1, 07L14KS, 08E06PD, 07441CS, 08E27MG, 08E23MG, 08E27MO, 08H19ND, 21DA02PA/2, 21DA02PA01, 5046853AA, TO36844AI, 09A12RB, 09D06NC, 7036844AI
- Generic paclitaxel 150 mg: N06846AC, WC16846AC, WO168461AC, W06846AC, XO26846AA, 07L19MA

Batch number of Gemzar (associated drug in both arms):

- Gemzar 1000 mg: 9RR64MA, A266138, A349957, A473303A, A494457C A659041C, A661706C, A674800C, A681542C, A740435K, 0496422A, 571229C, 6710A, 6735A A239661, A256450, A266152, A284807, A288297, A312162, A330198, A333603, A344655, A354077, A366667, A388588, A393029, A393413, A408841, A409753A, A416259A, A424662A, A429214, A431098, 1431131, A436856A, A447932A, A455917A, A4581413C, A460087D, A478178C, A499083A, A499274, A5989030, A614089C, A616742C, A627110, A640478, A641294A, A656713A, A680989D, A728674C, A912653A, O589423C, L03732, L04624, A670181D, A603795C, A677254C, L04500
- Gemzar 200 mg: FF5L13F, FF56A32A, FF6A32A, A349471, A447933A, A740435K, FF5L92P, A279403, A292547, A390374, A432381, A435287, 0473724A, 0A58791, A376976A, A497710, A635521C, A637420, A677273A, K8662, A781985, K8663D

Duration of treatment:

Patients continued the treatment until: documented disease progression, unacceptable toxicity or patient's refusal to continue.

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Criteria for evaluation:

Efficacy assessment: The primary efficacy endpoint was Progression-free Survival (PFS) (calculated from the randomisation date until the date of progression or death due to any cause whichever came first). PFS was established by an Independent Review Committee (IRC).

Secondary efficacy endpoints included the following:

- Tumour response rate: rate of confirmed CR + PR using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. The response rate was established by an IRC.
- Disease control rate: rate of CR+PR+Stable Disease ≥ 6 months.
- Time to first response: time to first CR or PR in patients with confirmed response.
- Duration of response: calculated among the responders (i.e., confirmed CR and PR) from the time that measurement criteria were first met for CR or PR until the date of progression or death due to any cause, whichever occurred first.
- Duration of disease control: calculated among the stable and responders (i.e., confirmed CR and PR) from the date of randomisation until the documentation of progression or death due to any cause.
- Time to treatment failure: calculated from the date of randomisation until the date of failure (progression, death, withdrawal due to adverse event, patient's refusal, lost to follow-up or initiation of new anti-cancer therapy).
- Overall survival: defined as the time elapsed from the date of randomisation up to death or last follow-up.

Health-related quality of life assessment:

Quality of life was assessed by the EORTC QLQ-C30 and QLQ-BR23 questionnaires. They were completed by the patient at baseline before randomisation, before cycle 2, and then every 2 cycles (i.e. before cycle 4, cycle 6, etc) and at the end of study treatment.

Safety assessment:

Clinical safety was assessed by:

- Complete history of malignant and non malignant disease.
- Full physical examination including vital signs, weight, PS.
- ECG at baseline.
- Regular reporting of adverse events graded according to the CTCAE version 3.0.
- The following laboratory tests were performed according to the study flow chart:

complete blood count: at screening then weekly i.e. at days 1, 8, 15 of each cycle.
serum chemistry: at screening then at day 1 of each cycle.

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Statistical methods:

Primary efficacy analysis

The primary efficacy analysis was the PFS in the ITT population using the IRC assessment of date of progression following the radiological and clinical review of data. In order to take into account the ICH guidelines, the confidence interval was also calculated on the per protocol population.

The hypothesis of non-inferiority in terms of PFS of vinflunine plus gemcitabine versus paclitaxel plus gemcitabine was to be accepted if the upper bound of the two-sided 95% confidence interval for the hazard ratio estimated from a stratified Cox proportional hazard model was smaller than 1.25. If non-inferiority was demonstrated in the first test, the hypothesis of superiority had to be tested with a type I error rate of 5% (i.e., no adjustment).

A stratified Cox proportional model was used with the following stratification factors: previous taxane-based chemotherapy, Karnofsky performance status, measurability of the disease and visceral involvement. Centre was not used in the analysis because of the high number of centres.

Secondary Efficacy analyses

Secondary efficacy analyses included Objective Response Rate, Disease Control Rate, duration of response and disease control and Overall Survival. Analyses of time to first response and time to treatment failure were also performed. These analyses were performed in the ITT population and in the per protocol population (except OS analysed in the ITT population only).

Sensitivity analyses of PFS were tested on both ITT population and per protocol population. Multivariate analyses of tumour response rate, progression-free survival, and overall survival were performed in order to take into account the pre-specified prognostic factors. These analyses were performed in the ITT population and were repeated in the per protocol population for the tumour response.

Descriptive subgroup analyses of PFS and overall survival were also performed according to previous taxane-based chemotherapy, KPS, measurability, visceral involvement and age at baseline.

Quality of Life analysis

The analysis of health-related quality of life was performed on the evaluable population for each QLQ (QLQ-C30 and QLQ-BR23).

Safety analysis:

The safety analysis was performed on the population evaluable for safety.

Safety assessments were based on medical review of adverse events (AEs), laboratory events, vital signs measurements and physical examinations. The following laboratory parameters were assessed throughout the study for all patients: haematological parameters (WBC count, ANC, platelets count, haemoglobin) and febrile neutropenia together with biochemical parameters assessing the liver function (ALT, AST, alkaline phosphatase, bilirubin); the renal function (creatinine) and the metabolic function (sodium, potassium, calcium). Worst CTCAE grade per patient and per cycle was presented.

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Summary – Conclusions:

Patient disposition:

	VFL + GEM		PTX + GEM		All	
	N	%	N	%	N	%
All Randomised patients (ITT population)	503	100	501	100	1004	100
All Treated patients	495	98.4	496	99.0	991	98.7
Eligible patients	495	98.4	489	97.6	984	98.0
Per protocol population*	421	83.7	455	90.8	876	87.3
Per protocol population (IRC)	382	75.9	423	84.4	805	80.2
Evaluable for quality of life – QLQ C30	323	64.2	362	72.3	685	68.2
Evaluable for quality of life – QLQ BR23	300	59.6	336	67.1	636	63.3

***** Per protocol population made of eligible and evaluable for efficacy patients who were treated in the arm assigned by randomisation

At the data-cut-off date for this report (30th June 2011) 176 (35%) patients in arm A were alive versus 170 (33.9%) in arm B and 15 (3.0%) patients in arm A were lost to follow-up versus 17 (3.4%) in arm B. In total, 98.7% of patients had discontinued the study treatment and 1.3% of patients were still under treatment: 6 patients (1.2%) in arm A and 7 (1.4%) in arm B.

The most common reason for treatment discontinuation in both groups was progressive disease, 37.6% in arm A and 39.5% in arm B. Patient's request was 16.1% in arm A and 13.2% in arm B. Discontinuation due to related adverse events was more frequent in arm A (16.3%) than in arm B (10.8%).

Patients characteristics at baseline:

The baseline characteristics and demographics were generally comparable between treatment arms with a minor imbalance for liver involvement (49.3% in VFL+GEM arm versus 44.5% in PTX+GEM arm).

ITT population	**VFL+GEM N=503**	**PTX+GEM N=501**	**ALL N=1004**
Age (years):			
Median [Range]	53.2 [24.1-77.7]	54.4 [21.5-79.0]	53.6 [21.5-79.0]
Mean (s.d)	53.1 (10.3)	54.0 (10.4)	53.5 (10.3)
Karnofsky performance status at baseline (N, %)			
100	175 (34.8)	185 (36.9)	360 (35.9)
90	229 (45.5)	221 (44.1)	450 (44.8)
80	78 (15.5)	83 (16.6)	161 (16.0)
70	21 (4.2)	11 (2.2)	32 (3.2)
40 *	-	1 (0.2)	1 (0.1)
Menopausal status (N, %)			
Menopaused	400 (79.5)	390 (77.8)	790 (78.7)
Not menopaused	97 (19.3)	104 (20.8)	201 (20.0)
Unknown	6 (1.2)	7 (1.4)	13 (1.3)

* Documented after patient's randomisation

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Disease characteristics:

ITT population	VFL + GEM (N=503)	PTX + GEM (N=501)	All (N=1004)
Main histopathological type (N, %)			
Ductal	362 (72.0)	381 (76.0)	743 (74.0)
Lobular	40 (8.0)	44 (8.8)	84 (8.4)
Mixed Ductal & Lobular	8 (1.6)	12 (2.4)	20(2.0)
Inflammatory	9 (1.8)	6 (1.2)	15 (1.5)
Carcinoma NOS	64 (12.7)	46 (9.2)	110 (11.0)
Others	19 (3.8)	10 (2.0)	29 (2.9)
Unknown	1 (0.2)	2 (0.4)	3 (0.3)
Stage at diagnosis (N, %)			
0	1 (0.2)	1 (0.2)	2 (0.2)
I	26 (5.2)	22 (4.4)	48 (4.8)
II	209 (41.6)	238 (47.5)	447 (44.5)
III	203 (40.4)	191 (38.1)	394 (39.2)
IV	1* (0.2)	-	1 (0.1)
Unknown	63 (12.5)	49 (9.8)	112 (11.2)
ER status (N, %)			
Positive	313 (62.2)	324 (64.7)	637 (63.4)
Negative	142 (28.2)	137 (27.3)	279 (27.8)
Unknown	48 (9.5)	40 (8.0)	88 (8.8)
HER-2 status (N, %)			
Negative	402 (79.9)	402 (80.2)	804 (80.1)
Unknown	98 (19.5)	97 (19.4)	195 (19.4)
Positive **	3 (0.6)	2 (0.4)	5 (0.5)
Prior chemotherapy (N, %)			
Anthracycline/anthracenedione***	493 (98.0)	490 (97.8)	983 (97.9)
Taxanes	170 (33.8)	168 (33.5)	338 (33.7)
Time from diagnosis to study entry (years)			
Median [Range]	3.4 [1.2-24.4]	3.6 [1.2-24.0]	3.5 [1.2-24.4]
Disease Free Interval (months			
Median [Range]	30.4 [0.0-242.8]	32.2 [1.8-227.7]	31.3 [0.0-242.8]
Disease extent at study entry (N, %)			
Metastatic	497 (98.8)	485 (96.8)	966 (97.8)
Visceral involvement	431 (85.7)	417 (83.2)	848 (84.5)

* Patient 060506. Protocol deviation.

** Documented after patient's randomisation

*** Anthracenedione accepted as prior anthracycline chemotherapy

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Efficacy results:

The primary objective of the trial was to show a non-inferiority in terms of Progression-Free Survival in the VFL+GEM arm versus PTX+GEM arm assuming a median PFS of 5.2 months in the control arm and 20% non-inferiority margin with a type I error of 0.05 and a 90% power.

A blinded external Independent Review Committee (IRC) was used to evaluate the tumour assessments of all patients and the date of progression.

The primary objective was achieved since PFS of patients in VFL+GEM arm was not inferior to the PFS of patients assigned to PTX+GEM: median PFS in ITT population, 8.0 months versus 8.4 months; (HR 1.05, 95% CI, 0.91 to 1.20) and in per protocol population, 8.2 months versus 8.3 months, (HR 0.99; 95% CI, 0.84 to 1.15). In the 2 datasets analysed, the upper bound of 95% CI of each HR is smaller than 1.25. Since non-inferiority was demonstrated, the hypothesis of superiority was tested without adjustments of the type I error and results showed that PFS of patients in VFL+GEM arm was not statistically superior to PTX+GEM arm (stratified log rank test, P=0.54).

For all the secondary efficacy parameters, assessed by IRC, the observed differences between arms were not statistically significant both in ITT and per protocol populations: ORR in ITT, 11.3% (95% CI 8.7 to 14.4) versus 14.6% (95% CI 11.6 to 18.0) (P=0.09) and ORR in the per protocol population, 14.9% (95% CI 11.5 to 18.9) versus 17.0% (95% CI 13.6 to 20.9) (P=0.32); DCR in ITT, 39.8% (95% CI 35.5 to 44.2) versus 44.9% (95% CI 40.5 to 49.4) (P=0.09) and DCR in per protocol population, 52.1% (95% CI 47.0 to 57.2) versus 52.5% (95% CI 47.6 to 57.3) (P=0.78).

There was no statistically significant difference in global health status for Quality of Life between the 2 study arms. Regarding the functional scales, the combination VFL+GEM produced an increase in physical functioning scale.

Overall survival was similar between the two arms: 18.9 months versus 19.1 months (HR=1.01, 95% CI, 0.87 to 1.20) (P=0.86). Same results were observed when OS was censored at initiation of new chemotherapy (18.6 months in VFL+GEM arm versus 21.1 months in PTX+GEM arm, HR= 1.08, 95%CI 0.85 to 1.36, P=0.52).

As a supportive analysis, PFS, ORR and DCR were also analysed by investigators' assessment. ORR was found to be significantly better in PTX+GEM arm than in VFL+GEM arm in ITT population, but no statistically significant differences were seen between arms in regard to ORR in per protocol population and DCR in both populations. PFS was statistically inferior for the VFL+GEM arm compared with PTX+GEM in both populations.

When the data were grouped by geographical regions, median PFS and OS were shown to be shorter in India than in overall population. Also, the differences between the 2 study arms tended to be greater in India in favour of PTX+GEM arm. The reverse was observed in Western Europe where median PFS was similar in both arms and OS tended to be longer in the VFL+GEM arm.

Extent of Exposure:

The median number of cycles was 6 in both arms.

The median relative dose intensity (RDI) of VFL and PTX was ≥90% while the proportion of patients who have received ≥90% of the planned dose was slightly higher with PTX than VFL (66.3% versus 63.4%). The median RDI of GEM was lower in arm A than in arm B (73.0% vs 86.6%) due to more frequent dose reductions/cancellations of day 8 GEM doses in arm A. It is noteworthy that the actual dose intensity of gemcitabine in the VFL+GEM arm was far below that of the PTX+GEM arm (median 497.6 mg/m^2/w versus 721.6 mg/m^2/w).

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Safety Results:

Myelosuppression was common as expected with the combination of both drugs. Overall, in VFL+GEM group, 93.1% of patients experienced neutropenia (all grades), and among them, 74.3% reported grade 3 or 4 neutropenia (grade 3: 27.3%, grade 4: 46.9%). Nevertheless, this event was rapidly reversible and not cumulative. Its clinical impact was limited since it led to discontinuation of 19 patients (3.9%), and was complicated by febrile neutropenia in 4.8 % of patients and by infections with severe neutropenia in 4.6% of patients.

In the PTX+GEM group, neutropenia (all grades) was reported by 88.5 % of patients, and among them 60% had a grade 3 or 4 (grade 3: 30.4%, grade 4: 29.6%). Similarly, its clinical impact was low as febrile neutropenia and infections with severe neutropenia were reported by 2.6% and 1.8% of patients respectively.

Grade 3-4 anaemia and thrombocytopenia tended to be slightly greater in the VFL+GEM arm but had no major clinical consequences.

The most common non-haematological AEs reported with VFL+GEM treatment were constipation (44.2%), nausea (48.3%), vomiting (38.8%), stomatitis (31.9%) and abdominal pain (25.3%). The most frequent grade 3-4 AEs were fatigue (14.5%), constipation (7.3%), and abdominal pain (5.9%). Grade 4 adverse events were rare. Incidence of these gastrointestinal events is similar to those reported with vinflunine single agent at 320 mg/m^2. Regarding constipation, among the 495 treated patients in arm A, 39.6% did not receive the recommended primary laxative prophylaxis as per protocol. Constipation occurred (all grades: 44.2 %) with a higher incidence in those patients who did not receive the laxative prophylaxis, but the incidence of severe cases was relatively low (grade 3: 6.9%, grade 4: 0.4%) and led to study treatment discontinuation in only 1.2% of patients. Constipation was not cumulative; it was reversible, easily manageable and was rarely reported beyond the 3rd cycle.

Grade 3-4 hyponatraemia has been reported in 12.6% of patients in VFL+GEM arm versus 6.8% in PTX+GEM arm.

However, multiple, alternative risk factors existed in most of the reported cases including gastrointestinal symptoms (vomiting, diarrhoea), use of diuretics and pre-existing renal impairment. Also, it should be noted that since a high percentage of patients treated with vinflunine may develop constipation, especially during cycle 1, infusion of hypotonic fluids for the treatment of constipation may be another important risk for hyponatraemia.

In the PTX+GEM arm, the most common non-haematological AEs were peripheral sensory neuropathy (44.2%), paraesthesia (14.9%), arthralgia (12.9%), alopecia (63.5%) and rash (11.1%) The most frequent grade 3-4 AEs were asthenia / fatigue (7.9%) and peripheral sensory neuropathy / paraesthesia (6.8%). Peripheral sensory neuropathy was mainly observed in the PTX+GEM group compared with the VFL+GEM group (54.8% vs 13.1%). Grade 3 was reported in 33 cases (6.7%) in the PTX+GEM group compared to only 4 cases (0.8%) in VFL+GEM group, who resolved after one dose reduction. No grade 4 cases were reported in both arms. In PTX+GEM arm, peripheral sensory neuropathy occurred in 43.8% of cycles.

Adverse events leading to discontinuation (regardless of relationship) were reported in 26.2% of patients in the VFL+GEM group and 18.2% of patients in the PTX+GEM group. The most common events were neutropenia/leukopenia, constipation/ileus, abdominal pain and fatigue in VFL+GEM group, and peripheral sensory neuropathy and fatigue in PTX+GEM group.

Overall, SAEs were reported in 43.2% of patients (study drug-related: 31.5%) in the VFL+GEM arm versus 25.8% (study drug-related: 11.3%) in the PTX+GEM arm.

There were 8 study drug-related deaths in VFL+GEM arm compared to 2 in PTX+GEM arm. Considering that out of the 8 deaths in VFL+GEM, in 4 patients at least one major protocol deviation was identified, the difference of study drug-related deaths between the 2 arms becomes smaller (0.8% versus 0.4%).

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Vinflunine	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **20', 20' – difluoro – 3', 4' - dihydrovinorelbine**	**Vol.: .....Page: .....**	

Conclusions:

The primary objective of this study which was to show a non-inferiority between the 2 study arms in terms of PFS was achieved, assuming a median PFS of 5.2 months in the control arm and 20% non-inferiority margin with a type I error of 0.05 and a 90% power. The primary analysis was performed in the intent-to-treat (ITT) population and was based on the data from the blinded review of the Independent Review Committee (IRC). Median PFS was 8.0 months in the VFL+GEM arm and 8.4 months in the PTX+GEM arm (HR 1.05, 95% CI [0.91 to 1.20]). Since the upper limit of the 95% CI for HR is below 1.25, non-inferiority was established.

ORR and DCR rate were not statistically significantly different in both the ITT and per protocol populations as per IRC.

There was no deleterious impact of chemotherapy on QoL in both study arms.

Overall survival analysis was conducted in the ITT population. Overall survival was similar in the two arms: 18.9 months in the VFL+GEM arm compared with 19.1 months in the PTX+GEM arm (HR = 1.01, 95% CI [0.87-1.19] (p=0.86). Importantly, the same proportion of patients received further treatment in the 2 study arms: 63.2% in the VFL+GEM arm vs 66.5% in the PTX+GEM arm.

Incidence of neutropenia was higher in VFL+GEM arm than in PTX+GEM arm, but without a major clinical impact. Vinflunine-induced constipation was manageable and its incidence was reduced when adequate prophylactic measures are followed.

Very few patients experienced neurotoxicity with the combination VFL+GEM, in contrast to patients with the combination PTX+GEM (13.1% versus 54.8%). Incidence of grade 3 neuropathy was 6.7 % in the PTX+GEM group compared to 0.8% (4 cases) in arm A. Peripheral sensory neuropathy was responsible for dose delays of paclitaxel (1.8%), and paclitaxel-alone dose reductions and cancellations in 5.8% and 3.7%, respectively. It lasted for about 1/3 of the total duration of treatment.

Overall, VFL+GEM can be seen as an alternate therapeutic option to the combination PTX+GEM combination, especially when considering the necessity to make available a treatment for a long period of time, slowing at maximum the risk of cumulative toxicity, especially paclitaxel-induced neurotoxicity, for this disease which is becoming increasingly a chronic disease.

Based on efficacy and safety results of VFL+GEM, compared to those of PTX+GEM, we can consider that the combination VFL+GEM offers a better clinical benefit/risk ratio based upon the reduced neurotoxicity for patients having failed an anthracycline frequently associated with a taxane and for whom a new but equally efficient treatment is still desirable.

Although the overall safety profile of VFL+GEM combination chemotherapy is acceptable, it could be improved further with the following recommendations:

- Good patient's selection with respect of the eligibility criteria,
- More compliance to the laxative and other prophylaxis regimens as indicated in the study protocol and also to the dose adjustment guidelines,
- Appropriate and immediate management of toxicities and optimal clinical follow-up of patient's status particularly during the early treatment period.

Date of report:

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