London, 25 September 2014
EMA/619399/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name Javlor

Procedure No. EMEA/H/C/000983/II/0011

Marketing authorisation holder (MAH): Pierre Fabre Médicament

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABC	Advanced Breast Cancer
AE	Adverse event
BID	bis in die
BSC	Best supportive care
CAPE	Capecitabine
CI	Confidence interval
CVL	Central venous line
D	Day
DDI	Drug-drug interaction
DLT	Dose limiting toxicity
DOXO	Doxorubicin
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
G-CSF	Granulocyte colony stimulating agent
GEM	Gemcitabine
Her2	Human epidermal receptor 2
IDMC	Independent Data Monitoring Committee
IV	Intravenous
IRC	Independent review committee
ITT	Intent to treat
KPS	Karnofsky performance status
MA	Marketing Authorisation
MBC	Metastatic breast cancer
MedDRA	Medical dictionary for regulatory activities
mL	Millilitre
MTD	Maximum Tolerated Dose
No	Number
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
PR	Partial response
PS	Performance status
PTX	Paclitaxel
QOL	Quality of life
R	Response
RD	Recommended Dose
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
s.d.	Standard deviation
SmPC	Summary of product characteristics

TCCU	Transitional cell carcinoma of the urothelium
TTP	Time to progression
VFL	Vinflunine
VRL	Vinorelbine
WBC	White blood cell count
WHO	World health organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pierre Fabre Médicament submitted to the European Medicines Agency on 4 June 2013 an application for a variation for an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Javlor	VINFLUNINE DITARTRATE	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication: in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve, previously treated with or resistant to an anthracycline and who are taxane resistant.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 20 November 2008. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Greg Markey Co-Rapporteur: Arantxa Sancho-Lopez

Submission date:	4 June 2013
Start of procedure:	21 June 2013
Rapporteur's preliminary assessment report circulated on:	12 August 2013
CoRapporteur's preliminary assessment report circulated on:	13 August 2013
PRAC RMP advice and assessment overview adopted by PRAC :	5 September 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2013
MAH's responses submitted to the CHMP on:	20 February 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	3 April 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	14 April 2014
PRAC RMP advice and assessment overview adopted by PRAC :	10 April 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2014
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 August 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 August 2014
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	4 September 2014
An Oral explanation took place on:	23 September 2014
CHMP opinion:	25 September 2014

2. Scientific discussion

2.1. Introduction

Breast cancer is the most common cancer in women in almost all countries. Despite a number of advances in recent years, it is still a leading cause of cancer death in women. Anthracyclines

(doxorubicin, epirubicin) and taxanes (paclitaxel and docetaxel) are the most active and widely used chemotherapeutic agents for breast cancer, but increased use of these agents at an early stage of disease often renders tumours resistant to these drugs by the time the disease recurs, thereby reducing the number of treatment options for metastatic disease. Drug resistance can occur due to various mechanisms, including modification of drug efflux membrane transporters as well as alterations in β-tubulin. Patients with disease progression or resistance to anthracyclines and taxanes may receive capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, but these offer limited duration of therapeutic activity. There remains a need for the development of new therapies for breast cancer patients whose tumours have progressed to become resistant to anthracyclines and taxanes. The goal of systemic therapy in such circumstances is to maximise control of symptoms, prevent serious complications, and prolong survival whilst maintaining quality of life. Treatment of recurrent, resistant metastatic breast cancer remains a major clinical challenge.

Javlor contains the active substance vinflunine ditartrate. It is an antineoplastic drug that belongs to the vinca alkaloid family. Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerisation into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis.

Javlor is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. Efficacy and safety of vinflunine have not been studied in patients with Performance Status ≥ 2.

Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy and is confined to units specialised in the administration of cytotoxic chemotherapy.

The recommended posology is 320mg/m² vinflunine as a 20 minute intravenous infusion every 3 weeks.

Javlor first received a marketing authorisation via the Centralised procedure in Europe on 21st September 2009.

This variation concerns an application for extension of the approved indications for Javlor. The MAH initially applied for the indication:

“Javlor in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant.”

During the procedure, the MAH amended the wording of the indication to better reflect the population in Study VFL 305 “Javlor is indicated in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve, and were previously treated with or resistant to an anthracycline and who are taxane resistant. “

2.2. Non-clinical aspects

2.2.1. Introduction

Non-clinical studies that were undertaken to support clinical trials or marketing application for Vinflunine have been previously reported as part of the marketing authorisation application (MAA) for Javlor (EMEA/H/C/000983). No new clinical data have been submitted in this application.

In accordance with Article of Directive 2001/83/EC, as amended, an update to the Javlor Environmental Risk Assessment has been provided by the Applicant.

2.2.2. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): vinflunine ditartrate			
CAS-number (if available): 162652–95-1			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD122	4.21	Potential PBT (N)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}	4.12	not B
	BCF	not required	B/not B
Persistence	DT50 or ready biodegradability	not required	P/not P
Toxicity	NOEC or CMR	not required	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	Value	Unit	Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.592 (default) 0.003226 (refined)	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Vinflunine ditartrate PEC $_{surfacewater}$ value has been refined with the market penetration factor (Fpen) by providing reasonably justified market penetration data. The PEC value using refined Fpen is 0.003226µg/L, below the action limit of 0.01 µg/L

Therefore vinflunine ditartrate is not expected to pose a risk to the environment.

2.2.3. Discussion on non-clinical aspects

After evaluating the available nonclinical data on the individual drug products, capecitabine and vinflunine and the potential for drug interactions, there is no evidence to suggest a possible pharmacology or pharmacokinetic interaction. Toxicology studies showed that both drugs (vinflunine

and capecitabine) target the immune system and a potential synergic effect could not be discarded. However, clinical data indicate that the combination does not suppose a significant higher risk for infections or haematological alterations that than VFL monotherapy in advanced breast cancer patients. In addition, alterations of the immune system are easily monitored in humans. Therefore, toxicology studies with the combination are not considered necessary. Genotoxicity and embryo-fetal development studies with the combination are not required because vinflunine has shown to be mutagenic, clastogenic and teratogenic. Likewise, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer according to the ICH S9 Guideline.

2.2.4. Conclusion on the non-clinical aspects

There are no new clinical data have been submitted in this application which was considered acceptable by the CHMP.

The use of the medicinal product Javlor, 25 mg/ml concentrate solution for infusion at 25 mg of vinflunine is unlikely to represent a risk for the environment when prescribed in the two requested indications and according to the Summary of Product Characteristics.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

However, a CHMP request for GCP inspection was adopted for the clinical study L00070 IN 305 B0 to confirm the robustness of the PFS methodology (primary endpoint), as the integrity of the pivotal study was questioned. Investigators adjudicated twice as many false progressions in the CAPE arm as in the VFL+CAPE arm.

GCP inspection - Summary

Three sites were inspected.

The findings for the three sites inspected were process related. However, these findings have been judged by the inspection team not to have any impact on the integrity, quality and trustworthiness of the data of the trial to any major extent, as well as, with no relevant impact on GCP compliance.

Based on the above, the data in the CSR presented as a whole, was considered from the inspection team perspective to be reliable and suitable for assessment in a variation application .

- Tabular overview of clinical studies *(**relevant studies for the claimed indication in bold**)*

Study number (abbreviation)	*Study*
L00070 IN 109 (VFL 109)	**A dose-finding and pharmacokinetic study of IV vinflunine in combination with capecitabine in metastatic breast cancer**
L00070 IN 206 (VFL 206)	Phase II study of IV vinflunine as second-line treatment of metastatic breast carcinoma after failure of anthracycline / taxane-based chemotherapy
L00070 IN 207 (VFL 207)	Phase II study of IV vinflunine as third-line treatment of metastatic breast carcinoma after failure of anthracycline / taxane-based chemotherapy
L00070 IN 212 (VFL 212)	Phase II study of IV vinflunine after failure of first-line vinorelbine-based regimen for advanced breast cancer
L00070 IN 303 (VFL 303)	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 305 (VFL 305)	**Phase III trial of vinflunine plus capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant**
L00070 IN 308 (VFL 308)	Phase III study in MBC patients, which compares VFL monotherapy at 280 mg/m² every 3 weeks with an alkylating agent of physician's choice in late-stage MBC who have failed an anthracycline, a taxane, an antimetabolite and a vinca-alkaloid

2.3.2. Pharmacokinetics

The currently approved SmPC includes data from the clinical pharmacology studies submitted with the original MAA and subsequent Type II variations to fulfil follow up measure (FUM) obligations. No specific new clinical pharmacology studies were carried out in support of this application.

Study VFL 109, a dose-finding and pharmacokinetic study of IV vinflunine in combination with capecitabine in metastatic breast cancer (previously assessed for FUM 009, June 2010) was conducted.

The clinical pharmacological aspects of vinflunine were assessed in the first application for Transitional cell carcinoma urothelium. The CHMP considered that the pharmacokinetic data submitted was satisfactory and the main PK characteristics had been adequately determined. The analytical methods were fully validated and were considered satisfactory. Satisfactory studies were performed to assess the distribution of vinflunine in the blood, its binding properties to blood components/plasma proteins and elimination. Metabolic pathways were appropriately identified, and the drug interactions studies were considered adequate. No healthy subject pharmacodynamic study reports were submitted. The pharmacodynamic properties of vinflunine were studied in cancer patient populations.

Overall, according to the Applicant, no pharmacokinetic interaction was observed in patients when vinflunine was combined with neither cisplatin, carboplatin, capecitabine, doxorubicin or gemcitabine. The studies VFL 109 and VFL 106 were previously assessed. The main characteristics of these studies are described below.

Phase I study of IV vinflunine in combination with Gemcitabine for treatment of advances Non Small Cell Lung Cancer in chemonaive patients. Two schedules of vinflunine were studied: day 1 every 3 weeks (schedule 1) and days 1 and 8 every 3 weeks (schedule 2). Results of schedule 1 were included in the original submission. The report submitted in December 2009 was completed with the results of schedule 2. Results of the combination of vinflunine plus gemcitabine in NSCLC patients whatever the schedule have no impact on data evaluation in bladder cancer patients treated with vinflunine montherapy. The pharmacokinetic analysis suggested that no effect of gemcitabine on the pharmacokinetics of vinflunine should be expected when drugs are co-administered regardless of the administration schedule. The effect of VFL on pharmacokinetics on gemcitabine could not be clearly established because of the small number of patients and the large intra-individual variability.

2.3.3. Pharmacodynamics

A single dose-finding and pharmacokinetic study of IV vinflunine in combination with capecitabine in metastatic breast cancer (VFL 109, see below) was carried out to determine the maximum tolerated dose and the recommended dose for further clinical investigation.

This study was originally assessed as part of FUM 009 (June 2010). The focus of the assessment at that time was the impact to patients with transitional cell carcinoma of the urothelial tract, treated with vinflunine monotherapy.

Mechanism of action

Vinflunine (VFL) is a microtubule inhibitor obtained by semi-synthesis using an original chemical approach in order to selectively modify the catharanthine moiety of the vinca-alkaloid scaffold. Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerisation into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis. *In vivo,* vinflunine displays antitumour activity against a broad spectrum of human xenografts in mice, both in terms of survival prolongation and tumour growth inhibition.

Primary pharmacology

Study VFL 109: Study title: A dose-finding and pharmacokinetic study of IV vinflunine in combination with capecitabine in metastatic breast cancer

Method

Study VFL 109 was an open, non randomised, multicentre dose finding and PK study of vinflunine in combination with capecitabine in patients with metastatic breast cancer. The first patient was enrolled on the 18th of September and the last patient on 27th February 2009. The clinical study report is dated 15th March 2010.

The Applicant claimed that the study was performed in compliance with Good Clinical Practice. The study was carried out at 4 centres in France. Patients were those who had a histologically confirmed diagnosis of breast adenocarcinoma and clear evidence of progressive metastatic disease, having previously received anthracycline and taxane based regimens.

Primary objective

The primary objective was to assess the maximum tolerated dose (MTD) of 2 different schedules and to determine for each the recommended dose (RD). The current recommended posology for VFL monotherapy is 320 mg/m² vinflunine as a 20 minute intravenous infusion every 3 weeks.

- The MTD was defined as the dose level at which at least 2 out of 3 or 2 out of 6 patients developed a dose limiting toxicity (DLT) during the first cycle. The RD was defined as the

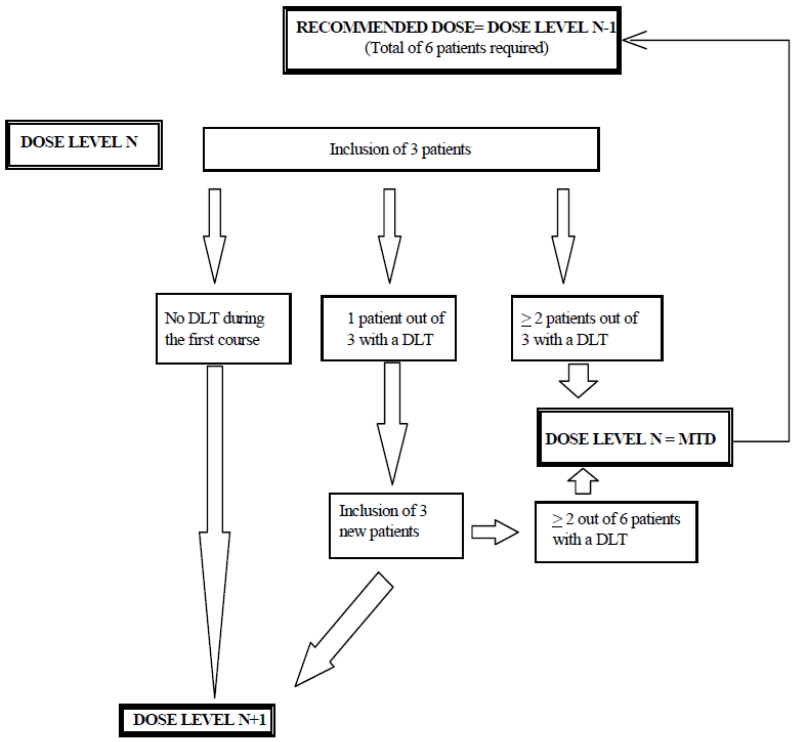
immediate lower dose. Dose escalation was performed according to the occurrence or not of DLT

- The DLT was defined as any of the following treatment-related adverse events occurring during the first cycle:
    - Neutrophils < 0.5 x 10^9 /L for > 7 days or < 0.1 x 10^9 /L for > 3 days
    - Platelets < 25 x 10^9/L or thrombocytopenia with bleeding or requiring platelet transfusion
    - Febrile neutropenia defined as absolute neutrophil count < 1.0 x 10^9 /L and fever > 38.5° C (fever of unknown origin without clinically or microbiologically documented infection CTC definition)
    - Any grade > 3 major organ toxicity according to the NCI CTC Version 2.0 (except alopecia or unpremedicated nausea/vomiting)
    - Treatment delay more than 2 weeks due to unresolved toxicity after the first administration.

Secondary objectives

Secondary objectives included the assessment of toxicities of the combination, investigation of the potential pharmacokinetic interaction when vinflunine and capecitabine are combined and assessment of the antitumour activity of the combination. Efficacy was determined according to RECIST and tumour assessment was performed every 2 cycles.

The dose escalation rules were:



Results

Schedule 1

In schedule 1, vinflunine was administered on day 1 every 3 weeks in combination with capecitabine administered BID from days 1 to 14 every 3 weeks. 16 patients were enrolled and treated in the first schedule.

Dose level	IV vinflunine (mg/m²) D1 Q 3 weeks	Oral capecitabine (mg/m²) BID D1 to D14 Q 3 weeks
1 A	280	825
2 A	320	825
3 A	280	1000

Number of registered, treated and evaluable patients

	1A		2A		3A		TOTAL	
	N	%	N	%	N	%	N	%
Registered patients	7	100.0	3	100.0	6	100.0	16	100.0
Treated patients	7	100.0	3	100.0	6	100.0	16	100.0
Evaluable patients for safety	7	100.0	3	100.0	6	100.0	16	100.0
Evaluable patients for MTD determination	7	100.0	3	100.0	6	100.0	16	100.0
Evaluable patients for efficacy	7	100.0	3	100.0	5	83.3	15	93.8

Dose limiting toxicities and recommended dose

At dose level 1A, 3 patients were treated without DLT. Two higher dose levels were investigated (3 patients in 2A and 6 patients in 3A) and identified as MTDs. Observed DLTs were G4 neutropenia, G3 & 4 anorexia, G3 & 4 fatigue, G3 constipation, G3 diarrhoea, G3 abdominal pain and febrile neutropenia. 3 patients discontinued because of adverse events, all of them were treated at the dose level 3A (hand-foot skin reaction, neutropenia and fatigue). Neutropenia was the main limiting toxicity of the combination, constipation, anorexia, fatigue, abdominal pain and diarrhoea were also reported. Febrile neutropenia occurred in 1 patient.

In schedule 1, the RD was considered to be 1A; vinflunine 280 mg/m² on day 1 and capecitabine 825 mg/m² BID on days 1 to 14, every 3 weeks (total of 7 patients treated at this dose level).

Efficacy

Among the 16 patients treated, 15 were evaluable for efficacy in terms of response. No information is available on PFS or OS. 4 partial responses were observed at dose level 1A, 2 at dose level 2A and 1 at dose level 3A. 7 patients (43.8 %) had stable disease and disease control (PR + SD) was achieved in 14 patients (87.5 %).

Response	1A		2A		3A		ITT	
	N = 7	%	N = 3	%	N = 6	%	N = 16	%
PR	4	57.1	2	66.7	1	16.7	7	43.8
SD	3 42.	9	1	33.3	3	50.0	7	43.8
PD	-	-	-	-	1	16.7	1	16.7
NE	-	-	-	-	1	16.7	1	16.7

Pharmacokinetics (PK)

No firm conclusions can be made from a PK perspective regarding the effect of Capecitabine (CAPE) on the pharmacokinetics of VFL or VFL on CAPE.

Schedule 2

In schedule 2, vinflunine was administered on days 1 and 8 every 3 weeks in combination with capecitabine administered BID from day 1 to 14 every 3 weeks. 23 patients were enrolled and treated in the second schedule

Dose level	IV vinflunine (mg/m²) D1 and D8 Q 3 weeks	Oral capecitabine (mg/m²) BID D1 to D14 Q 3 weeks
1B	150	825
2B	170	825
3B	1000	170
4B	190	1000
5B	210	1000

Dose limiting toxicities by dose level

Dose level	N° patients	N° patients with DLT	Type of DLT
1B	4	1	G3 fatigue
2B	2	1	G3 constipation
5B	4	3	neutropenic infection G4 neutropenia ≥ 7 days G3 constipation G3 febrile neutropenia

Dose limiting toxicities and recommended dose

At dose level 1B and 2B, 1 patient out of 3 experienced a DLT. Three higher dose levels were investigated and 5B was identified as MTD. DLT were G3 fatigue, G3 constipation, neutropenic infection, G4 neutropenia, G3 constipation and G3 febrile neutropenia.

In schedule 2, the RD was considered to be 4B; vinflunine 190 mg/m^2 on days 1 and 8 + CAP 1000 mg/ m^2 BID on days 1 to 14, every 3 weeks (total 8 patients were treated at this dose level).

Efficacy

The 23 patients treated were evaluable for efficacy. Partial responses (PR) were reported in 9 patients (39.1%) and 8 patients (34.8%) had stable disease according to the investigator's assessment. Disease control was 73.9 % (17 patients).

Pharmacokinetics

No firm conclusions can be made from a PK specific regarding the effect of CAPE on the pharmacokinetics of VFL or the effect of VFL on CAPE.

2.3.4. Conclusions on clinical pharmacology

Observed dose limiting toxicities for the combination were neutropenia, febrile neutropenia, neutropenic infection, anorexia, fatigue, constipation, diarrhoea and abdominal pain. The dose selected for further clinical investigation was schedule 1, dose level 1A; vinflunine 280 mg/m² on day 1 and capecitabine 825 mg/m² BID on days 1 to 14, every 3 weeks (total of 7 patients treated at this dose level before initiation of the phase III study).

In light of the available PK data from study VFL 109, it was concluded at the time of the assessment of FUM009 that, although the submitted data did not require an update to the product information, drug-drug interaction between vinflunine and capecitabine could not be fully excluded. .

2.4. Clinical efficacy

2.4.1. Dose response study

Dose selection for the phase III study VFL 305 was based on the results of the dose-finding study VFL 109 (see above).

2.4.2. Main study

VFL 305

Study VFL 305 was an open, randomised, two-arm, multinational phase III study comparing the combination of VFL+CAPE with CAPE in patients with locally advanced or metastatic breast cancer who had received prior anthracycline and who are resistant to taxane. Patients might have received up to a maximum of 3 prior chemotherapy regimens including neoadjuvant/adjuvant chemotherapy.

The Applicant stated that this phase III 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.

Methods

Study participants

Inclusion criteria
Written informed consent personally signed and dated before completing any study-related procedure
Women with histologically or cytologically confirmed carcinoma of the breast
Documented locally recurrent or metastatic disease not amenable to curative surgery or radiotherapy
Patients must have received either one, two or three prior chemotherapy regimens including those administered in the neoadjuvant or adjuvant setting. Note: neoadjuvant treatment followed by adjuvant treatment (amendment PA03) were counted as a single regimen; hormonal anti-cancer agents and non-traditional cytotoxic agent such as trastuzumab were not counted as chemotherapy regimens when administered alone.
Prior treatments must have included both an anthracycline and a taxane given as either monotherapy or as part of a combination with another agent and might have been included in the same regimen. These agents might have been given in either the neo or adjuvant or the metastatic setting or both
Patients must have received a minimum cumulative dose of anthracycline (≥ 180 mg/m² of doxorubicin or ≥300 mg/m² of epirubicin) or be resistant to an anthracycline (to be applied to doxorubicin, epirubicin and liposomal doxorubicin) (amendment PA03) according to the following criteria: a. Tumour progression while on anthracycline or within 4 months of the last anthracycline dose when given in the metastatic setting*or, b. Recurrence while on anthracyclines or within 12 months of the last anthracycline dose when given in the adjuvant or neoadjuvant setting*. * Note: in addition to these criteria, to be considered resistant, a patient must have received at least 2 cycles of an anthracycline-based regimen.
Patients must be resistant to taxane therapy: a. Tumour progression while on taxane or within 4 months of last taxane dose when given in the metastatic setting or**, b. Recurrence while on taxanes or within 12 months of the last taxane dose when given in the adjuvant setting or neoadjuvant setting**. ** Note: in addition to these criteria, to be considered resistant, a patient must have received at least

2 cycles of a taxane-based regimen. (amendment PA03) Prior anti-cancer hormone therapy was allowed but the patient must no longer be candidate for hormone therapy. The treatment must have been terminated 2 weeks prior to randomisation
Patients who had been treated with anti HER-2 targeted therapy must have discontinued therapy at least 3 weeks prior to randomisation (amendment PA03)
Prior radiation therapy was allowed to < 30% of the bone marrow and must have been completed at least 4 weeks before randomisation (amendment PA04)
Patients with measurable or non measurable disease defined according to revised RECIST guideline (version1.1) (amendment PA01)
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
Estimated life expectancy ≥12 weeks
Karnofsky performance score ≥70 %,
Age ≥21 years and < 80 years (amendment PA04)
Adequate haematological function as defined by absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x10^9/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 the case of liver metastases, alkaline phosphatase ≤ 5 x ULN (within 7 days before first study treatment)
Adequate renal function as defined by a calculated creatinine clearance ≥50 mL/min according to Cockroft-Gault formula (mL/min) = [(0.85)(140- age)(weight)]/[(0.81)(SrCr µmol/L)] (within 7 days before first treatment administration)
ECG without clinically relevant abnormality (within 7 days before first treatment administration)
Patients on coumadin or warfarin must have been on stable doses and have an International Normalized Ratio (INR) ≤ 3 at the time of screening (amendment PA03)
Women of childbearing potential must have been using a medically accepted method of contraception to avoid pregnancy during the 2 months preceding the start of study treatment and must have had a negative serum or urine pregnancy test within 72 hours prior to first treatment administration
The patient must have had access to social insurance if applicable in the local regulations
Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
Exclusion criteria
Patients with known or with clinical evidence of brain metastasis or leptomeningeal involvement
Patients with pulmonary lymphangitis or symptomatic pleural effusion (grade ≥2) that resulted in pulmonary dysfunction requiring active treatment
Patients having 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, and other malignancy treated at least 5 years previously with no evidence of recurrence
Patients with pre-existing motor/sensory peripheral neuropathy of CTCAE Version 3.0 grade >1
Patients having received > 3 regimens of chemotherapy
Prior therapy with capecitabine and/or vinca-alkaloids (including vinflunine)
History of severe hypersensitivity to vinca alkaloids and/or to fluoropyrimidine or any contra indication to any of the study drugs
Known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency
Pregnant or breast feeding women
Positive pregnancy test at inclusion
Known history of HIV infection
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 affected the absorption of capecitabine (malabsorption syndrome, 2/3 gastric resection and bowel resection)
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

Treatment

The recommended doses of vinflunine and capecitabine in combination were established in the phase I trial VFL 109. In VFL 305, patients were randomised to receive to either:

Experimental treatment arm - Arm A (TEST):

- Vinflunine (Pierre Fabre Medicament) 280 mg/m² as a 20-minute IV infusion on day 1 of each cycle repeated every 3 weeks
- Capecitabine 825 mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks (self-administered)
- Antiemetic prophylaxis (dexamethasone 8 mg or equivalent just before each infusion) and constipation prophylaxis (dietary measures and laxatives from day 1 to day 5 of each cycle) were predetermined in the study protocol
- Doses modifications for vinflunine (280 mg/m², 250 mg/m², 225 mg/m²) and capecitabine (825 mg/m² bid, 660 mg/m² bid, 500 mg/m² bid) according to haematological and non-haematological toxicities were predetermined in the study protocol

Control arm - Arm B (REFERENCE):

- Capecitabine (Xeloda, Roche) 1250 mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks (self-administered)
- Doses modifications for capecitabine (1250 mg/m² bid, 950 mg/m² bid, 625 mg/m² bid) according to haematological and non-haematological toxicities were predetermined in the study protocol
- The innovator capecitabine product is Xeloda (Roche) and the breast cancer indication is: Xeloda in combination with docetaxel (see section 5.1) is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Compliance

The administration of study treatment was carried out at the investigational centre and supervised by a physician or a nurse from the department for vinflunine infusion and Day 1 of capecitabine. The investigator and/or the pharmacist performed pill counts on return supplies of capecitabine. In order to improve the compliance, a patient leaflet was given to the patients.

Duration of treatment

Treatment was administered until disease progression or withdrew from study (unacceptable toxicity or other reasons). Treatment could be delayed up to 2 weeks and dosing of VFL and/or CAPE could be reduced twice to allow for resolution of toxicity.

Concomitant medication

The patient must not have received other investigational drugs and/or anti-cancer treatment while on study. Authorised ancillary treatments were given as medically indicated including anti-emetics, anti-diarrhoea and analgesics. Authorised concomitant treatments were:

- Anti-emetics (steroids) given according to the protocol
- Steroids not to be routinely given except as anti-emetics
- Radiotherapy use for bone pain in palliative setting
- Bisphosphonate therapy at the discretion of the investigator
- Opiates in case of pain. In this case, prophylactic use of laxatives was recommended
- Concomitant prophylactic use of colony stimulating factors was not allowed except in case of febrile neutropenia and then in prophylactic intent for further cycles,
- Erythropoietin according to institutional practice

Dose adjustment

Dose adjustment and/or treatment delay were to be made in case of haematological and/or non-haematological toxicities

Crossover

No crossover to vinflunine was allowed from the CAPE arm.

Objectives

The primary objective was to show superiority in terms of PFS, assuming a median PFS of 3 months in the control arm and a 30% increase in the VFL+CAPE arm, with a type I error of 0.05 and 90% power. The primary analysis was planned to occur when 615 events (progression or death) had been recorded. The study had 80% power of detecting a 25% increase in median overall survival, assuming a median overall survival of 10 months in the control arm (minimum of 631 events required).

Outcomes/endpoints

The primary endpoint was PFS and secondary endpoints included OS, response rate, disease control rate, the time to response and duration of response, the time to treatment failure, safety and quality of life (EORTC QLQ-C30 & QLQB23 questionnaires).

The endpoints in the study and their definitions are listed in the table below:

Primary Endpoint	Description of Endpoint
Progression-free survival	PFS was defined from the time elapsed from the date of randomisation until the date of progression or the death (whatever the reason of death). Tumour assessment was requested every 6 weeks (+/- 3 working days) from randomisation (regardless of the timing of treatment cycles) until disease progression was documented The PFS was primarily analysed in the Intent-to-treat (ITT) population,

	Independent Review Committee (IRC) and based on RECIST version 1.1. Patients lost to follow-up, or without a known record of progression or death at time of analysis had the progression-free survival censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression, whichever occurs last.
Secondary Endpoints	**Description of Endpoint**
Overall survival	Measured as the duration between the date of randomisation and the date of death from any cause. For those patients not dead at the time of analysis, survival duration was censored at the date of last contact if lost to follow-up or at the date of last news.
Tumour response rate (overall response rate, ORR)	Defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) as best overall (across all time points) response from the date of randomisation until disease progression but within 30 days from the last administration. Confirmation of response was not requested.
Duration of response	Measured from the first time that measurement criteria were first met for objective response (documented CR or PR) until recurrence/progression or death whatever the cause
Disease control rate (DCR)	Defined as the proportion of patients who achieved at least a stabilisation of the disease not counting patients with only non-measurable disease at baseline and best overall response of non-CR/non-PD
Time to treatment failure	Time to treatment failure was measured from the randomisation to the date of failure (disease progression, relapse, death, patient's withdrawal, protocol violation, lost to follow-up or start of a new anti-tumoural treatment). Patients who reached the time point of analysis without failure as defined above had the time to treatment failure censored at the date of last tumour assessment or last contact of a follow up not showing progression. Patients who discontinued treatment for other reason and were lost to follow-up were censored at the date of last contact.
Quality of life	Completion of QLQ-C30 and QLQ-BR23 (breast specific) questionnaires The questionnaires had to be completed within 24 hours prior to randomisation, before cycle 3 and then every 2 cycles and at the end of treatment evaluation. Patients were considered evaluable for health-related quality of life analysis if they completed at least 2 questionnaires (including the questionnaire completed prior to randomisation).
Safety	
Reporting of Adverse Events and Serious Adverse Events Adverse Events Of Special Interest (AEOSI)	Any adverse or intercurrent event occurring during the study period, spontaneously reported by the patient or observed by others, was to be recorded on the AE pages of the CRF, regardless of the relationship to the study medications. The sponsor identified categories of AEs expected with the combination treatment

Sample size

The final analysis required at least 615 events (progression or death), which is the number of events needed for a two sided, log-rank test at an alpha = 0.05 significance level and a 90% power to show a statistically significant difference when the true hazard ratio is 0.77 (median PFS in the test arm is 30% greater than median PFS of 3 months in the control arm (CAPE - Xeloda SmPC). An expected total number of 764 patients had to be randomised. A minimum of 631 deaths were required for the analysis of OS to have an 80% power of detecting a 25% increase in median survival in patients who received VFL+CAPE, based on a median OS of 10 months in the CAPE alone arm.

Randomisation

Treatment and randomisation number were allocated to each patient using an Interactive Voice Response System (IVRS). Randomisation was stratified by: Karnofsky PS (90-100 versus 70-80), Resistance to anthracycline (yes versus no), Disease measurability (measurable versus non measurable), Number of prior chemotherapy lines given in the metastatic setting (0 versus 1 versus > 1) and Site.

Blinding (masking)

This was an open label study.

Statistical methods

Statistical analyses were performed by the Biostatistics Department at IRPF. The final analysis of PFS was to be conducted once the required number of events (615 progressions or deaths) had been observed. The primary efficacy population was the intent-to-treat (ITT) population. PFS analyses were carried out using the IRC assessment of date of progressions, including radiological and clinical review of data. The hypothesis of superiority in terms of PFS of VFL+CAPE vs. CAPE was to be accepted if the p-value from a stratified log-rank test was smaller than 0.05.

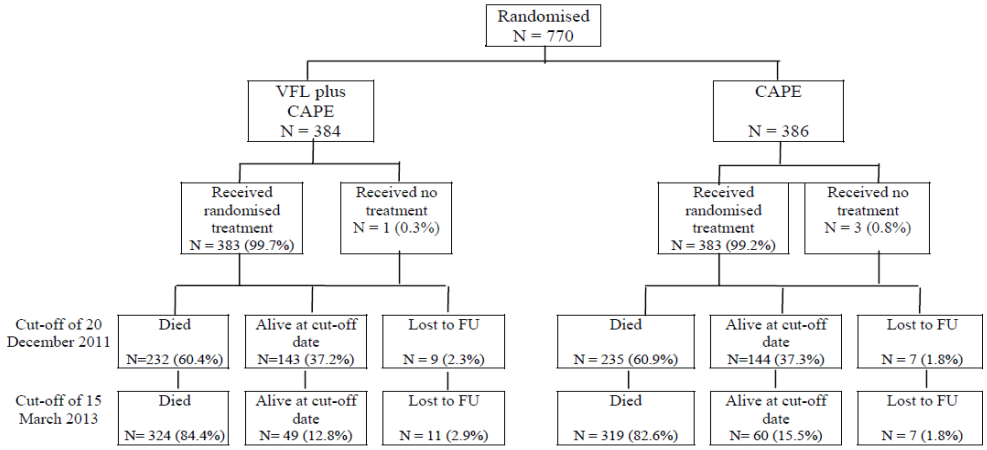
Population Analysed

- Intent-To-Treat population (ITT): The primary population for the analysis of the efficacy results was the ITT population which included all randomised patients whether they received study treatment or not and analysed in the arm they were assigned by randomisation.
- Eligible population: The eligible population was made of all randomised patients who had no predefined major protocol deviations from inclusion/exclusion criteria and analysed in the arm they were assigned by randomisation. The eligible population was used for ancillary analyses of PFS and OS.
- Per-protocol population: The per protocol population was composed of all eligible patients, treated in the arm assigned by randomisation and with no predefined major deviation during the study. The per protocol population was used for ancillary analyses of PFS and OS.
- Evaluable population for response: The evaluable for response population was a subset of the eligible population who included all randomised and treated patients who were evaluable for response and analysed in the arm assigned by randomisation. To be evaluable, a patient had to have received at least 2 cycles of treatment unless progression or death due to progression and to have been evaluated at least once after the second cycle. The evaluable for response population was used for an ancillary analysis of response only.

- Evaluable population for safety: All treated patients were included in the safety analysis and were analysed in the treatment arm they actually received.
- Evaluable patients for health-related quality of life assessment had all completed one questionnaire (at least two thirds of the questions) within fourteen days prior to randomisation, and at least one questionnaire during the study period, just before the third cycle of study treatment.

Results

Participant flow



Source: CSR L00070 IN 305: Appendix 16.2.1, Table 1-2, 1-2 (2nd cut-off of 15 March 2013), 1-11

Recruitment

The first patient was enrolled on the 6th of May 2009 and the last patient was enrolled on the 25th of May 2011 (129 active centres in 21 countries). High recruiting countries (> 10%) were Belarus, France, India, Russia and Ukraine.

Conduct of the study

Protocol amendments

Four substantial amendments were made to the initial version of the protocol. Among these 4 substantial amendments, 3 were of general purpose, while one (PA02) was a local amendment for Spain (correction of translation mistakes from English to Spanish).

Amendment PA01; General and Substantial

This amendment was issued prior to the enrolment of the first patient (9th March, 2009). The main modifications were:

- Implementation of the revised RECIST guideline version 1.1 (instead of the previous version 1.0)

- Introduction of systematic anti-emetic prophylaxis guidelines
- Modification of constipation prophylaxis
- Deletion of unnecessary biological exams such as prothrombin time or partial Thromboplastin time, replaced by the INR for patients on coumadin or warfarin
- Modification of treatment labelling

Amendment PA03; General and Substantial

This amendment was issued after the start of the enrolment in the study (7th December, 2009). The main modifications were:

- Modification of recommendations for capecitabine dose adjustment for consistency with a new version of Xeloda SmPC
- Minimum delay between discontinuation of the anti-HER-2 therapy and randomisation shortened from 4 to 3 weeks
- Clarification of inclusion criteria about resistance to taxane therapy (restricted to patient with at least 2 cycles of taxane-based therapy)
- Clarification about acceptable imaging based procedures for confirmation of bone lesions (CT-scan, MRI and X-ray)
- Addition of dose adaptation rules for total bilirubin level increase
- Update of the number of expected participating countries and sites

Amendment PA04; General and Substantial

This amendment was issued after the start of the enrolment in the study (19th May, 2011).

The main modifications were:

- Modification of the inclusion criteria, limiting the inclusion to patients of less than 80 year-old in agreement with recent results and modification of the Javlor SmPC
- Modification of secondary efficacy analysis with pooling of 3 independent factors (hormonal receptor to oestrogen status, hormonal receptor to progesterone status and HER-2 status) for PFS, OS and ORR multivariate analysis.

Protocol deviations

A total of 57 deviations concerning 53 patients with at least 1 predefined major eligibility deviation were identified. The most frequent eligibility deviations identified were the absence of resistance to taxanes (3.9% of all randomised patients, 15 patients in each arm) and the absence of resistance to anthracyclines with no minimum cumulative dose received (1.9%). Two patients in each treatment group received prior vinca-alkaloid.

	VFL + CAPE n (%)	CAPE n (%)
No of patients	384	386

Pre-defined Major Eligibility Protocol Deviation - ITT Population		
Number of major eligibility deviations	26 (6.8)	31 (8.0)
No cytologically/histologically confirmed breast carcinoma	-	1 (0.3)
No anthracycline or absence of resistance or minimum cumulative dose not reached	6 (1.6)	9 (2.3)
No resistance to taxanes	15 (3.9)	15 (3.9)
KPS < 60	1 (0.3)	-
Brain metastasis or leptomeningeal involvement	-	1 (0.3)
Pulmonary lymphangitis or symptomatic pleural effusion	-	2 (0.5)
History of second primary malignancy within 5 years	1 (0.3)	1 (0.3)
Prior therapy with capecitabine and/or vinca-alkaloids	3 (0.8)	2 (0.5)
Major Protocol Deviations On Study per Patient - ITT Population		
Number of patients with at least one other major protocol deviation on study	20 (5.2)	4 (1.0)
Treatment by other anti-neoplastic agent during study treatment	3 (0.8)	4 (1.0)
Treatment by concurrent use of strong inhibitor of CYP3A4	17 (4.4)	-

Minor Protocol Deviations

265 patients in arm A (69.0%) and 233 in arm B (60.4%) encountered at least one minor protocol violation at study entry or on study. The most frequent minor protocol deviations were related to ECG 'not done', done > 7 days before first administration or with clinically relevant abnormality (12.5% vs 11.9%) and treatment with another experimental/anticancer therapy within 30 days prior to randomisation [stopped before 1st administration] (8.6% vs 10.9%).

Baseline data

Study VFL 305 - Patient and disease characteristics at baseline			
	VFL+CAPE (N = 384)	CAPE (N = 386)	All (N = 770)
Median age [range]	53.6 [27.0-80.6]	54.0 [26.8-77.7]	53.7 [26.8-80.6]
	n (%)	n (%)	n (%)
WHO performance status			

0	253 (65.9)	247 (64.0)	500 (64.9)
1	130 (33.8)	138 (35.8)	268 (34.8)
2	1 (0.1)	1 (0.1)	2 (0.3)
Stage at diagnosis			
0 - I	44 (11.5)	18 (4.7)	62 (8.1)
II	132 (34.4)	128 (33.2)	260 (33.8)
III	145 (37.8)	164 (42.5)	309 (40.1)
IV	51 (13.3)	69 (17.9)	120 (15.6)
Unknown	12 (3.1)	7 (1.8)	19 (2.5)
Histology at diagnosis			
Ductal	283 (73.7)	273 (70.7)	556 (72.2)
Lobular	29 (7.6)	40 (10.4)	69 (9.0)
Other	29 (7.6)	19 (4.9)	48 (6.2)
Carcinoma NOS(1)	43 (11.2)	54 (14.0)	97 (12.6)
Hormonal receptor status(2)			
ER and / or PgR +ve	221 (57.6)	217 (56.2)	438 (56.9)
ER and PgR negative	151 (39.3)	157 (40.7)	308 (40.0)
Unknown	12 (3.1)	12 (3.1)	24 (3.1)
Her-2 status(2)			
Her-2 negative	287 (74.7)	287 (74.4)	574 (74.6)
Her-2 positive	66 (17.2)	75 (19.4)	141 (18.3)
Unknown	31 (8.1)	24 (6.2)	55 (7.1)
Triple negative(3)	103 (26.8)	106 (27.5)	209 (27.1)
Locally advanced	10 (2.6)	13 (3.4)	23 (3.0)
Metastatic	374 (97.4)	373 (96.6)	747 (97.0)
Visceral involvement(4)	297 (77.3)	292 (75.6)	589 (76.5)
No of organs involved			
1	71 (18.5)	83 (21.5)	154 (20.0)
2	123 (32.0)	126 (32.6)	249 (32.3)
> 3	190 (49.5)	177 (45.9)	367 (47.7)

(1) NOS : not otherwise specified mainly reported in Russia, Ukraine and Belarus for 85.6% of carcinoma NOS, (2) test done in local laboratory, (3) ER negative, PgR negative and Her-2 negative, (4) liver, lung, pleura, heart, peritoneum, spleen and suprarenal glands

Neoadjuvant / adjuvant chemotherapy n (%)			
Neoadjuvant only	59 (15.4)	51 (13.2)	110 (14.3)
Adjuvant only	167 (43.5)	177 (45.9)	344 (44.7)
Neo + adjuvant	57 (14.8)	62 (16.1)	119 (15.5)
Chemotherapy for advanced disease			
No of regimens n(%)			
0	79 (20.6)	77 (19.9)	
1	178 (46.4)	191 (49.5)	369 (47.9)
2	116 (30.2)	105 (27.3)	221 (28.7)
3	11 (2.9)	13 (3.4)	24 (3.1)
Median number of prior chemotherapy regimens			
Median No of regimens [range]	2 [1-4]	2 [1-3]	2 [1-4]
Chemotherapy agent n (%)			
Anthracyclines			
Cumulative dose (1)	340 (88.5)	326 (84.5)	666 (86.5)
Resistance(2)	244 (63.5)	240 (62.2)	484 (62.9)
Taxanes(3)			
Resistance	369 (96.1)	371 (96.1)	740 (96.1)
Non-resistance(4)	15 (3.9)	15 (3.9)	30 (3.9)
(1) doxorubicin > 180 mg/m², epirubicin > 300 mg/m², (2) doxorubicin, epirubicin, liposomal doxorubicin, (3) paclitaxel, docetaxel, (4) major protocol deviation			
Disease Characteristics at Study Entry			
Time from diagnosis to study entry (years) Median [range]	2.4 [0.2-21.2]	2.1 [0.2-31.5]	2.2 [0.2-31.5]
Treatment-free interval- months: Median [Range]	1.4 [0.0-16.5]	1.4 [0.0-15.8]	1.4 [0.0-16.5]
Time from previous chemotherapy to study entry – months Median [Range]	2.5 [0.4-57.3]	2.3 [0.4-42.2]	2.4 [0.4-57.3]
Patients with other prior antineoplastic therapy			

Hormone therapy n(%)	209 (54.4)	186 (48.2)	395 (51.3)
Trastuzumab n(%)	17 (4.4)	26 (6.7)	43 (5.6)
Bevacizumab n(%)	52 (13.5)	45 (11.7)	97 (12.6)
Protein kinase inhibitors (Lapatinib, sorafenib, sunitinib)	11 (2.9)	14 (3.6)	25 (3.2)
Medical History			
Cardiac disorders – Any	48 (12.5)	65 (16.8)	113 (14.7)
Arteriosclerosis coronary artery	7 (1.8)	8 (2.1)	15 (1.9)
Coronary artery disease	15 (3.9)	15 (3.9)	30 (3.9)
Myocardial infarction and ischemia	6 (1.6)	18 (4.7)	24 (3.1)
Cardiac failure	6 (1.6)	7 (1.8)	13 (1.7)
Cardiomyopathy	18 (4.7)	11 (2.8)	29 (3.8)
Conduction disorders	1 (0.3)	4 (1.0)	5 (0.7)

Numbers analysed

The primary population for the analysis of efficacy results was the ITT population, defined as all randomised patients whether they were treated or not and assigned in the arm they were assigned to by randomisation.

Study VFL 305 - Summary of analysed populations

	VFL + CAPE n (%)	CAPE n (%)
Randomised (ITT)	384 (100)	386 (100)
Treated patients (safety population)	383 (99.7)	383 (99.2)
Eligible population	359 (93.5)	358 (92.5)
Per protocol population	341 (88.8)	356 (92.2)
Evaluable for response (IRC)	313 (81.5)	316 (81.9)

Outcomes and estimation

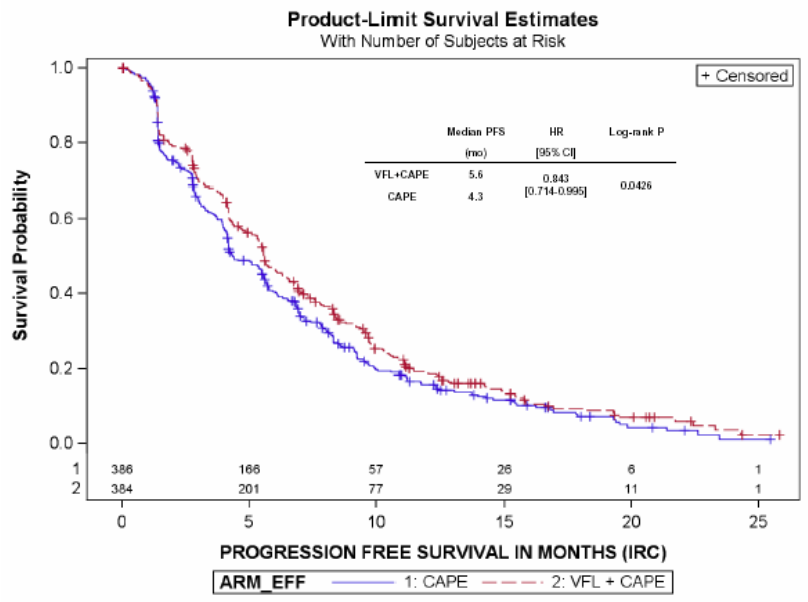
Primary Endpoint

Progression-Free Survival (PFS)

The primary analysis was performed on the IRC dataset from the radiological and clinical blinded evaluation of the progression dates in the ITT population. Median PFS was of 5.6 months for the VFL+CAPE arm and 4.3 months for the CAPE arm, the HR was 0.84, 95% CI 0.71-0.99; P=0.0426.

	VFL+CAPE N = 384	CAPE N = 386
No. of events	314	312
No. of censored (%)	70 (18.2)	74 (19.2)
Median PFS in months [95% CI]	5.6 [5.3 – 6.3]	4.3 [4.1 – 5.6]
HR [95% CI]	0.84 [0.71 – 0.99(2)]	
P value(1)	0.0426	
(1) stratified log rank test (2) 95% CI inferior value=0.995		

Study VFL 305 - Progression-free survival in the ITT population as per IRC – Cut-off of 20 December 2011



Patient's Status for PFS IRC in the ITT Population - Cut-Off of 20th December 2011

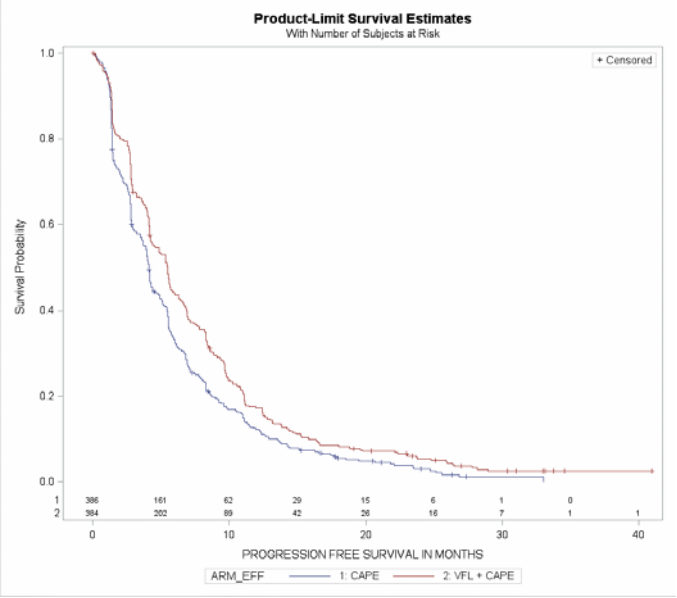
Censored observations for PFS	Patients status for PFS	VFL+CAPE N = 384 N (%)	CAPE N = 386 N (%)
No	Progression on study	116 (30.2)	141 (36.5)
	Progressing during follow-up	140 (36.5)	106 (27.5)
	Death for progression	50 (13.0)	53 (13.7)
	Death for related toxicity	2 (0.5)	1 (0.3)
	Death for other reason	6 (1.6)	11 (2.8)
Yes	Alive without progression	70 (18.2)	74 (19.2)

ITT population assessed by the investigator (cut-off dates 20th December 2011 and 15th March 2013)

- Based on the cut-off of 20th December 2011, the median PFS according to the investigator was of 5.5 months for the VFL+CAPE arm and 4.1 months for the CAPE arm (HR= 0.77, 95%CI 0.661-0.903; P=0.0012)

- Based on the cut-off of 15th March 2013, the median PFS according to the investigator was of 5.5 months for the VFL+CAPE arm and 4.1 months for the CAPE arm (HR= 0.77, 95%CI 0.66-0.90; P=0.0007)

VFL 305 - Progression-free survival in the ITT population as per investigator - Cut off of 15 March 2013



Summary of PFS results in the ITT population – IRC and investigator

	IRC assessment Cut-off of 20 December 2011		Investigator assessment Cut-off of 20 December 2011		Investigator assessment Cut-off of 15 March 2013	
	VFL + CAPE (N = 384)	CAPE (N = 386)	VFL + CAPE (N = 384)	CAPE (N = 386)	VFL + CAPE N = 384	CAPE N = 386
No events	**314**	**312**	**334**	**352**	366	368
No censored (%)	70 (18.2)	74 (19.2)	50 (13.0)	34 (8.8)	18 (4.7)	18 (4.7)
Median (months)	**5.6**	**4.3**	**5.5**	**4.1**	**5.5**	**4.1**
[95% CI]	[5.3-6.3]	[4.1-5.6]	[4.4-5.7]	[3.7-4.4]	[4.5 - 5.7]	[3.8-4.4]
Hazard ratio [95% CI]	0.84 [0.71-0.99]		0.77 [0.66-0.90]		0.77 [0.66 - 0.90]	
P value	0.0426		0.0012		0.0007	

Secondary Endpoints

Overall survival

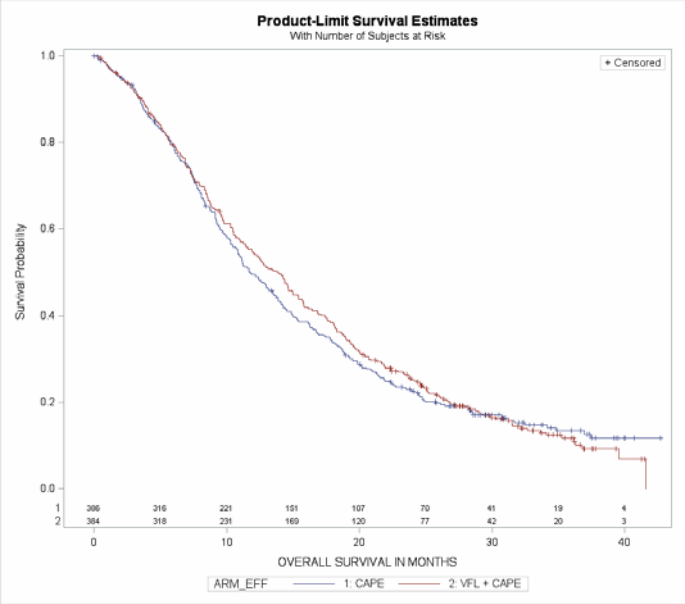
Cut-off: March 15th, 2013

The final analysis of survival was conducted in the ITT population after 643 deaths had been observed (equivalent of 84.4% of patients in the VFL+CAPE arm, 82.6% in the CAPE arm). The median OS was 13.9 months in the VFL+CAPE arm and 11.7 months in the CAPE single agent arm, difference 2.2 months (HR 0.98, 95%CI 0.83-1.15; P=0.7657).

Overall Survival - ITT Population - Cut-Off of 15 March 2013

	VFL+CAPE N = 384	CAPE N = 386
No. of events	324	319
No. of censored (%)	60 (15.6)	67 (17.4)
Median OS in months [95% CI]	13.9 [11.9 – 15.0]	11.7 [10.8 – 13.5]
HR [95% CI]	0.98 [0.83 – 1.15]	
P value(1) (1) stratified log rank test	0.7657	

Overall survival in the ITT population - Cut off of 15th March 2013



Patient's Status for OS in the ITT Population - Cut-Off of 15 March 2013

Censored observations for OS	Patients status for OS	VFL+CAPE N = 384 N (%)	CAPE N = 386 N (%)
No	Death for progression	310 (80.7)	299 (77.5)
	Death for related toxicity	2 (0.5)	1 (0.3)
	Death for other reason	10 (2.6)	19 (4.9)
	Death with reason not specified	2 (0.5)	-
	Alive	49 (12.8)	60 (15.5)
Yes	Lost to follow up	11 (2.9)	7 (1.8)

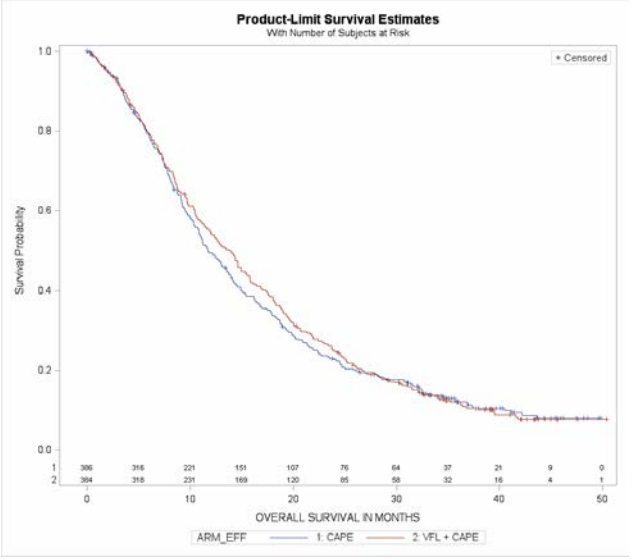
Updated analysis (December 19th, 2013)

An updated analysis of overall survival was performed on December 19th, 2013. An updated analysis has provided 31 additional events and HR 0.97 (0.83-1.14), p value 0.6976. The overall survival updated confirms the previous reported results of 2.2 months' median survival advantage favouring VFL+CAPE with a reduction of risk of death of 3% [HR (95% CI): 0.97 (0.83-1.14)], this difference being not statistically significant.

Table X14: Overall Survival: ITT population (Cut-off: December 19th, 2013)

	VFL+CAPE N = 384	**CAPE N = 386**
No. of events	337	337
No. of censored (%)	47 (12.2)	49 (12.7)
Median OS in months [95% CI]	13.9 (11.9 - 15.0)	11.7 (10.8 – 13.5)
HR [95% CI]	0.97 (0.83 - 1.14)	
P value	0.6976	

Figure 3: Overall survival: ITT population (Dec 19th, 2013)



Objective response rate (CR+PR) assessed by IRC showed a slight trend in favour of the VFL+CAPE arm (22.9% vs. 17.9%) and the disease control rate (CR+PR+SD) was 57.3% in the VFL+CAPE arm compared to 47.9% in the CAPE arm.

Tumour response

Tumour response was evaluated by RECIST version 1.1.

ITT population	VFL+CAPE	CAPE
No of patients	384	386
Objective response rate (CR+ PR) (%)	22.9	17.9
[95% CI]	[18.8-27.5]	[14.2-22.1]
P value	0.1030	
Disease control rate (CR + PR+ SD) (%)	57.3	47.9
[95% CI]	[52.2-62.3]	[42.9-53.0]
P value	0.0089	

Tumour Response as per IRC Regardless of the Nature of the Lesions in the ITT and Evaluable for Response Populations

	ITT population		Evaluable for response population	
	VFL+CAPE	CAPE	VFL+CAPE	CAPE
No of patients(N):	384	386	313	316

Best response - N (%):				
CR	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
PR	87 (22.7)	68 (17.6)	73 (23.3)	61 (19.3)
SD	132 (34.4)	116 (30.1)	120 (38.3)	110 (34.8)
Non-CR/non-PD(1)	45 (11.7)	62 (16.1)	39 (12.5)	54 (17.1)
PD	86 (22.4)	98 (25.4)	80 (25.6)	90 (28.5)
Non-evaluable	33 (8.6)	41 (10.6)	-	-
Overall Response Rate(2)%(95%CI)	22.9 (18.8-27.5)	17.9 (14.2-22.1)	23.6 (9.0-28.8)	19.6 (15.4-24.4)
	0.1030		0.1030	
Disease Control Rate(3) % (95% CI)	57.3 (52.2-62.3)	47.9 (42.9-53.0)	62.0 (56.4-67.4)	54.4 (48.8-60.0)
P-value(4)	0.0089		0.0509	
(1) Non-CR/non-PD for non-measurable lesions (2) CR+PR (3) CR+PR+SD (4) Cochran-Mantel-Haenszel test				

Tumour Response as per IRC in Patients with Measurable Lesions in the ITT Population

	ITT population	
	VFL+CAPE	CAPE
No of patients with measurable lesion (N):	322	306
Best response - N (%):		
Complete Response (CR)	-	1 (0.3)
Partial Response (PR)	87 (27.0)	68 (22.2)
Stable Disease (SD)	132 (41.0)	116 (37.9)
Progressive Disease (PD)	83 (25.8)	91 (29.7)
Non-evaluable (NE)	20 (6.2)	30 (9.8)
Overall Response Rate(1) % (95% CI)	27.0 (22.2-32.2)	22.6 (18.0-27.7)
P-value(3)	0.2670	
Disease Control Rate(2) % (95% CI)	68.0 (62.6-73.1)	60.5 (54.7-66.0)

P-value(3)	0.0462	
(1) CR+PR (2) CR+PR+SD (3) Cochran-Mantel-Haenszel test		

Time to Response, Duration of Response, Duration of Disease Control and Time to Treatment Failure as per IRC in the ITT Populations

ITT Population	IRC Assessment	
	VFL+CAPE	CAPE
Median time to First Response (1) (mo) (95% CI)	2.2 (1.1-13.4)	2.6 (1.1-9.6)
Duration of Response (mo) (95% CI)	8.4 (4.9-9.3)	5.5 (4.1-6.9)
Duration of Disease Control (mo) (95% CI)	6.9 (6.0-8.3)	6.8 (5.7-7.2)
Time to Treatment Failure		
No. of events	354	366
No. of censored (1) (%)	30 (7.8)	20 (5.2)
Median TTF in months (95% CI)	4.2 [4.1-4.8]	3.6 [2.8-4.0]
HR (95% CI)	0.80 [0.69-0.93]	
P value(2)	0.0040	
(1) alive patients without failure (2) stratified log rank test		

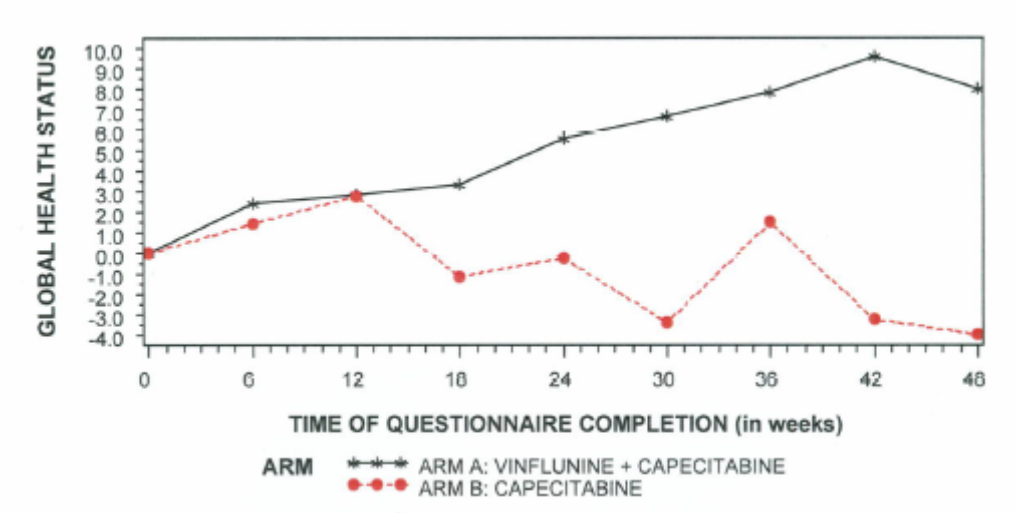
Clinical benefit

A clinical benefit was calculated for treated patients with a performance status (PS) and/or weight assessed at baseline and at least once assessed during the treatment period. There was no relevant change of PS over time between the 2 treatment groups. Weight loss was more frequent in the VFL+CAPE arm (30.4% compared to 19.7%).

Quality of life

The EORTC QLQ-C30 and QLQ-BR23 questionnaires were to be completed before randomisation, before cycle 3 and then every 2 cycles. A total of 256 patients (66.7 %) in the VFL plus CAPE arm and 239 patients (61.9 %) in the CAPE arm were evaluable for quality of life.

Change in the global health status score in the evaluable patients for quality of life QLQ-C30



Ancillary analyses

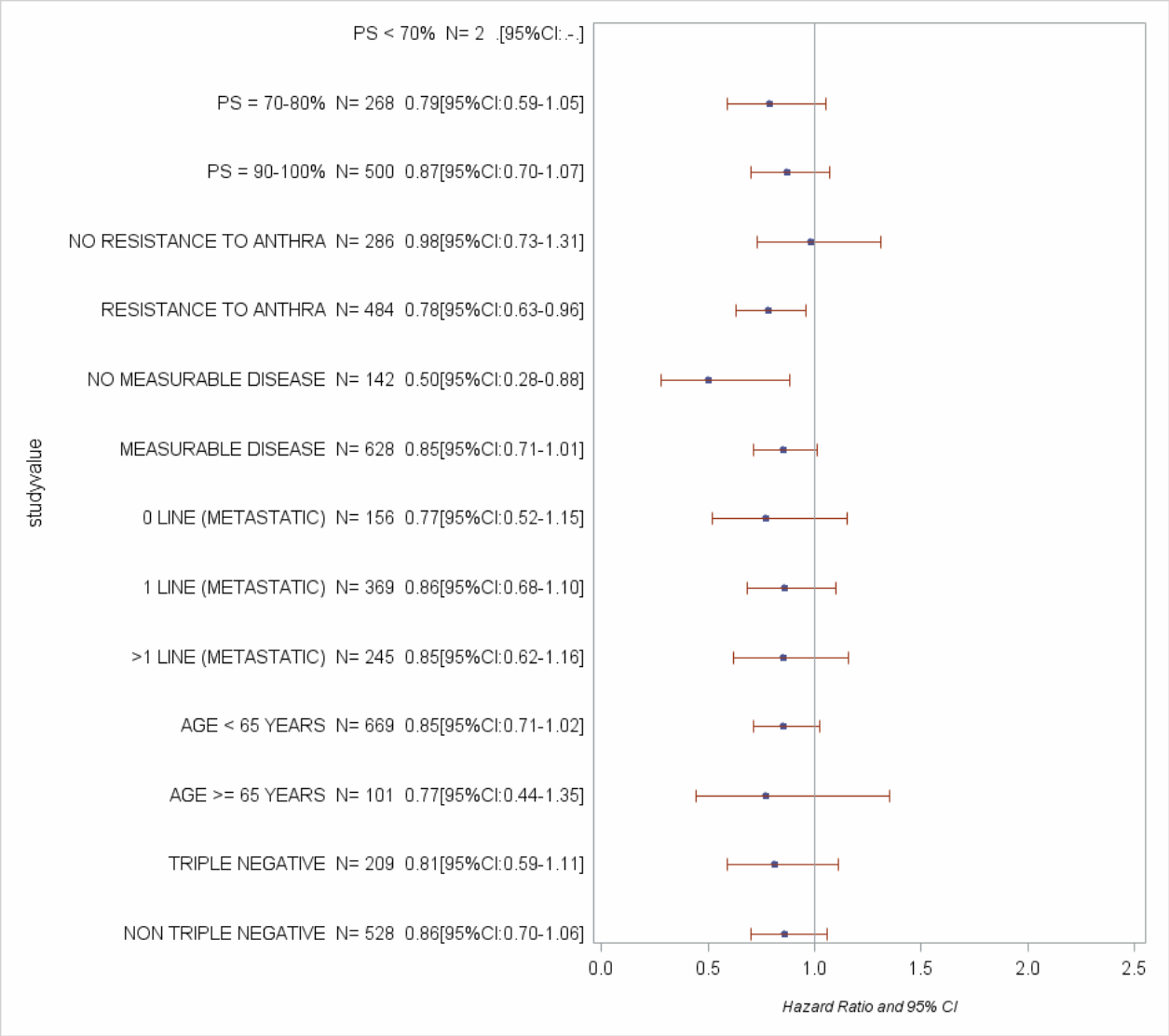
A multivariate analysis conducted in the ITT population with a Cox's proportional hazard model was performed using the following prognostic factors: age, post-menopausal status, number of organs involved, time from initial diagnosis to randomisation, prior hormone therapy, prior neoadjuvant/ adjuvant chemotherapy, and hormone receptors and HER-2 status.

Multivariate analysis of progression-free survival in the ITT population - Cut off of 20 December 2011

Prognostic factor (1)	Hazard ratio [95% CI]	P value (2)
IRC - assessed PFS		
Triple negative disease	0.64 [0.53 - 0.78]	< 0.0001
Number of organs involved	0.70 [0.59 - 0.84]	0.0001
Age	0.77 [0.60 - 1.00]	0.0461
Time from initial diagnosis to randomisation	0.79 [0.63 - 0.95]	0.0132
Investigator-assessed PFS		
Treatment arm	0.77 [0.66 - 0.90]	0.0014
Number of organs involved	0.85 [0.72 - 1.01]	0.0637
Menopausal status	0.82 [0.69 - 0.98]	0.0252
Triple negative versus other	0.65 [0.54 - 0.78]	< 0.0001

Subgroup analyses
Predefined subset analyses of PFS are shown below.

Subset analyses of progression-free survival as per IRC in the ITT population at the cut-off of 20 December 2011



Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial VFL 305

Title: A phase III trial of vinflunine plus capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant	
Study identifier	L00070 IN 305 B0 - VFL 305

Design	Open-label, randomised, two-arm, multinational study Date of first enrolment was 6th May 2009 The cut-off date for primary endpoint analysis was 20th December 2011 The cut-off date for overall survival was 15th March 2013		
Primary objectives	The primary objective was to show a superiority in terms of PFS assuming a median PFS of 3 months in the control arm and a 30% increase in the VFL plus CAPE arm with a type I error of 0.05 and a 90% power.		
Treatments groups	Test N = 384	Vinflunine 280 mg/m² as a 20-minute IV infusion on day 1 of each cycle repeated every 3 weeks + Capecitabine 825 mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks	
	Control N = 386	Capecitabine 1250 mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks	
Results and Analysis (ITT population)			
Endpoints		VFL+CAPE N = 384	CAPE N = 386
PFS IRC median in months [95% CI]		5.6 [5.3 – 6.3]	4.3 [4.1 – 5.6]
HR [95% CI] & P value		0.84 [0.71 – 0.99] p- 0.0426	
Overall survival		13.9 [11.9 – 15.0]	11.7 [10.8 – 13.5]
HR [95% CI] & P value		0.98 [0.83 – 1.15] p - 0.7657	
Objective response rate (%)[95% CI]		22.9 [18.8-27.5]	17.9 [14.2-22.1]

Supportive studies

Phase II studies of VFL monotherapy

Study VFL 206

This was a phase II, open-label, multicentre, single-arm study of IV vinflunine in the second-line treatment of patients with metastatic breast cancer previously treated with an anthracycline and a taxane. The study was carried out in 15 centres and the first subject was enrolled 4th March 2002 and the date of last completed patient was 17th May 2005. Patients had a histological diagnosis of metastatic breast adenocarcinoma with clear evidence of progressive disease, and had received an

anthracycline and a taxane. The primary objective was to evaluate the response rate according to modified WHO criteria. Secondary objectives were duration of response, progression-free survival, overall survival, safety profile and pharmacokinetic profile of VFL over the first 2 cycles. Vinflunine was administered at 320 mg/m² every 3 weeks.

Results

60 patients were treated and 51 were for evaluable for efficacy.

- After independent panel review (IPR), an objective response rate of 30.0% [95% CI: 18.9 – 43.2] according to WHO criteria was achieved in the ITT analysis
- Median PFS was 3.7 months [2.8-4.2]
- Median OS was 14.3 months [9.2-19.6]

Study VFL 207

This was a phase II, open-label, multicentre, single-arm study of IV vinflunine in the third-line treatment of patients with metastatic breast cancer previously treated with an anthracycline and a taxane. The study was carried out in 22 centres and the first subject was enrolled 4th January 2002 and the date of last completed patient was 19th April 2005. Patients had a histological diagnosis of metastatic breast adenocarcinoma with clear evidence of progressive disease. The primary objective was to evaluate the response rate according to modified WHO criteria. Secondary objectives were duration of response, progression-free survival, overall survival, safety profile and pharmacokinetic profile of VFL over the first 2 cycles. Vinflunine was administered at 320 mg/m² every 3 weeks

Results

55 patients were treated and 43 were for evaluable for efficacy.

- After the independent review, an objective response rate of 12.5% [95% CI: 5.2 - 24.1] was achieved in the whole population
- Median PFS was 2.6 months [1.6-4.0]
- Median OS was 11.4 months [7.4-14.2]

Study VFL 212

This was a phase II, open-label, multicentre, single arm study of IV vinflunine in the second-line treatment of patients with advanced breast cancer previously treated with vinorelbine. The study was carried out in 4 centres and the first subject was enrolled 1st October 2003 and date of last completed patient was 1st July 2009. Patients had histologically or cytologically confirmed breast carcinoma and evidence of advanced disease. The primary objective was to evaluate the response rate according to RECIST (version 1.0). Secondary objectives were duration of response, progression-free survival, overall survival and safety profile. VFL was administered at 320 mg/m² every 3 weeks.

Results

38 patients were treated and 36 were evaluable for efficacy.

- 3 partial responses were observed (7.9%)
- 24 disease stabilisations (63.2%)
- Median PFS was 4 months [2.5-6.1]
- Median OS was 13.6 months [8.7-18.9]

2.4.3. Discussion on clinical efficacy

This application for vinflunine in combination with capecitabine in breast cancer patients is supported by a single pivotal trial, VFL 305. The study was an open, randomised, two-arm, multinational study comparing the combination of VFL+CAPE with CAPE in patients with locally advanced or metastatic breast cancer who had received prior anthracycline and who were resistant to taxane. The primary endpoint was PFS and secondary endpoints included OS, response rate, disease control rate, the time to response and duration of response, the time to treatment failure, safety and quality of life (EORTC QLQ-C30 & QLQB23 questionnaires). In CHMP scientific advice, the company was strongly encouraged to use OS as the primary endpoint, with PFS reported as a secondary endpoint. The Applicant failed to follow this advice. The dose selection for study VFL 305 was based on the results of the dose-finding study VFL 109. Observed DLTs for the combination were neutropenia, febrile neutropenia, neutropenic infection, anorexia, fatigue, constipation, diarrhoea and abdominal pain. The ultimately selected regimen had a more favourable toxicity profile; no febrile neutropenia, no severe infection or no grade 3 - 4 non haematological toxicities. The Applicant's rationale for the posology is accepted, though it is noted that only 7 patients have been treated at the selected dose level, before initiation of the phase III study. A lower dose of capecitabine was utilised in the VFL+CAPE arm, compared to the CAPE arm. In CHMP scientific advice, the company's stated position was that the use of a different capecitabine dose, leads to the assumption that if the superiority hypothesis of PFS is confirmed, this effect will be assigned to vinflunine. The CHMP considered the dose reduction rationale and choice of dose reasonable and that the possible loss of efficacy associated with a reduced dose of CAPE would need to be overcome by vinflunine in order to demonstrate superiority.

The indication initially applied for was not in line with the inclusion and exclusion criteria of study VFL 305. Therefore, during the procedure, the MAH amended the wording of the indication to better reflect the population in Study VFL 305 "Javlor is indicated in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve, and were previously treated with or resistant to an anthracycline and who are taxane resistant. Efficacy and safety of vinflunine have not been studied in patients with locally advanced or metastatic breast cancer with Karnofsky performance score < 70%".

In relation to GCP, no critical findings were uncovered and most findings were process related. Overall, the GCP inspection found that the data in the CSR were considered to be reliable and suitable for assessment in a variation application.

No explanation could be found for the inconsistency observed between the IRC and the investigators, except for the fact that the assessments by the IRC and the patient's investigator were performed in different conditions.

A total of 770 patients with locally advanced or metastatic breast cancer were randomised, 384 patients in the VFL+CAPE arm and 386 patients in the CAPE arm. Demographics and disease characteristics were generally well-balanced between the 2 treatment groups. The primary analysis was performed on the IRC dataset in the ITT population. The addition of vinflunine to capecitabine reduced the risk of progression or death by 16%. Median PFS was 4.3 months in the CAPE arm and 5.6 months in the VFL+CAPE arm, median difference 1.3 months (HR 0.84 95% CI : 0.71 - 0.99, P = 0.0426). The magnitude of effect is considered to be small. In addition, the statistical significance is not very compelling and the Applicant is referred to the CHMP points to consider on applications with one pivotal study (CPMP/EWP/2330/99), where it is expected that statistical evidence considerably stronger than $p<0.05$ is usually required, particularly as there is no supportive data from phase II studies in the claimed population and posology.

A similar magnitude of effect was seen in terms of median PFS between the primary analysis of IRC and median PFS as assessed by investigators. However, of note is the difference observed in terms of the number of events reported by the IRC assessment and the investigator assessment (20 more events in the VFL+CAPE arm by investigator & 40 more events in the CAPE arm by investigator. The Applicant has attempted to justify the discrepancies between investigators and the IRC, and has shown that the results are still positive when taking a conservative approach and incorporating the 'worst case' from the two assessments into the analysis. Median OS was 13.9 months in the VFL+CAPE arm and 11.7 months in the CAPE arm, difference 2.2 months (HR 0.98, 95% 0.83 - 1.15, P = 0.7657). The most common reported cause of death was progressive disease. More patients in the combination arm died due to progression (80.7% vs 77.5%) and more patients died for other reasons not related to either disease progression or toxicity in the CAPE arm (4.9% in the CAPE arm vs. 2.6% VFL + CAPE arm). An updated analysis has provided 31 additional events and with a cut-off of 19th December 2013, HR 0.97 (0.83-1.14), p value 0.6976. The positive trend of 2.2-months median survival advantage favouring the VFL+CAPE was observed for both analyses

Objective response rate (CR+PR) assessed by IRC showed a slight trend in favour of the VFL+CAPE arm (22.9% vs. 17.9%) and the disease control rate (CR+PR+SD) was 57.3% in the VFL+CAPE arm compared to 47.9% in the CAPE arm. Median time to first response was numerically shorter in the VFL+CAPE arm and duration of response was longer (8.4 vs 5.5 months). No difference was observed between the 2 arms regarding the duration of disease control. Median TTF was slightly longer in the VFL+CAPE arm (4.2 vs 3.6 months). A continuous improvement in the global health status score was apparently observed for the VFL+CAPE arm.

2.4.4. Conclusions on the clinical efficacy

The proposed new indication is supported by a single pivotal study. The effect on PFS, the primary endpoint, is modest (HR: 0.84, 95% CI: 0.71-0.99, P = 0.046) and there is no significant effect on overall survival (HR: 0.97, 95% CI: 0.83-1.14, P = 0.6976) or other important secondary endpoint e.g. response rate; 22.9% vs. 17.9%, P = 0.1030. The results from study VFL 305 are not considered to be statistically compelling for the purposes of a marketing authorisation application.

2.5. Clinical safety

2.5.1. Introduction

All patients who received at least one dose of study drug were included in the adverse events (AE) tables. If an AE was reported more than once during treatment, the greatest severity was used for tabulation. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. Safety definitions:

- An Adverse Event (AE) - defined as any new untoward medical occurrence or worsening of a pre-existing medical condition regardless of a causal relationship with treatment occurring at any time after patient's formal entry into the study until the follow up period as defined in the respective study protocols
- A serious AE (SAE) was defined as an AE that met any of the following criteria: resulted in death; was life-threatening; required hospitalisation or prolongation of existing inpatient hospitalisation; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect. Other events including cancer, overdosage, pregnancy and any relevant adverse experience or abnormal laboratory value occurring during the study period were also considered as SAEs
- Treatment Emergent Signs and Symptoms (TESS) were considered for analysis of adverse events in study VFL 305. A TESS was defined as any event that first occurred during the treatment period (i.e. from first drug administration date up to last administration date + 30 days) or that "worsened" during that study period.
- Adverse events of special interest; identified categories of AEs that may either be expected with the use of cytostatics or *vinca* alkaloids, with a focus on VFL
    - Febrile Neutropenia, Infections with severe neutropenia, Constipation, Ileus, Intestinal obstruction, Abdominal pain, Nausea, Vomiting, Stomatitis or mucositis, Diarrhoea, Myocardial Infarction/ ischaemia, Cardiac arrhythmias, Cardiac conduction disorders, Local injection/infusion site reactions, Extravasation, Peripheral sensory neuropathy, Peripheral motor neuropathy, Fatigue, Myalgia, Immediate hypersensitivity Syndrome of inappropriate anti-diuretic hormone secretion (SIADH), Hepatic dysfunction, Posterior reversible encephalopathy syndrome (PRES)

Patient exposure

383 patients in the VFL+CAPE arm and 383 in CAPE arm received at least one dose of the study treatment (any of the study drugs in the combination arm). The median number of cycles per treated patient was 6.0 in the VFL+CAPE arm and 5.0 in the CAPE arm. The total number of cycles received at the time of cut-off for the primary analysis ranged from 1 to 35 in the VFL+CAPE arm and 1 to 33 in CAPE arm.

Extent of exposure to study drugs

	VFL+CAPE (N = 383)		CAPE (N = 383)
	VFL	CAPE	CAPE
Dose (mg/m²)	280	825	1250

No cycles	3011		2560
No cycles with VFL	2970		-
No cycles with CAPE	2990		2560
Median number cycles	6		5
[range]	[1-35]		[1-33]
Relative dose intensity (%)			
Median	98.6	94.1	92.1
[range]	[67.7-105.0]	[7.4-107.4]	[18.4-106.4]
Cumulative dose and dose intensity for capecitabine			
Median dose intensity per patient (mg/m²/wk)[min, max]	7 259.1 [572.9-8 302.3]		10 742.5 [2 145.7-12 417.4]

Adverse events

Overall, 94.0% of patients in the VFL+CAPE arm (related AE recorded in 79.6%) and 90.1% of patients in the CAPE arm (related AE recorded in 73.6%) experienced at least one adverse event (AE).

Overall incidence of treatment emergent AEs - Study VFL 305

Treatment arm	VFL + CAPE (N = 383) n (%)	CAPE (N = 383) n (%)
AEs	360 (94.0)	345 (90.1)
AEs reported as drug-related	305 (79.6)	282 (73.6)
Serious AEs	103 (26.9)	83 (21.7)
Serious AEs reported as drug-related	51 (13.3)	23 (6.0)
AEs leading to discontinuation - related	27 (7.0)	25 (6.5)
Deaths*	26 (6.8)	32 (8.4)
Death reported as drug-related	2 (0.5)	1 (0.3)
* death occurring within 30 days of the last study drug administration		

Common treatment-emergent AEs regardless the relationship-VFL plus CAPE

Treatment arm	VFL + CAPE (N = 383) N (%)		CAPE (N = 383) N (%)	
	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
Blood and lymphatic system disorders	94 (24.5)	57 (14.9)	42 (12.8)	21 (5.5)
Cardiac disorders	28 (7.3)	2 (0.5)	21 (5.5)	1 (0.3)
Eye disorders	22 (5.7)	0	30 (7.8)	0
Gastrointestinal disorders	256 (66.8)	56 (14.6)	220 (57.4)	41 (10.7)
General disorders and administration site conditions	244 (63.7)	52 (13.6)	166 (43.3)	29 (7.6)
Hepatobiliary disorders	27 (7.0)	6 (1.6)	20 (5.2)	5 (1.3)
Infections and infestations	93 (24.3)	10 (2.6)	86 (22.5)	5 (1.3)
Investigations	168 (43.9)	7 (1.8)	123 (32.1)	3 (0.8)
Metabolism and nutrition disorders	67 (17.5)	13 (3.4)	52 (13.6)	14 (3.7)
Musculoskeletal and connective tissue disorders	150 (39.2)	23 (6.0)	101 (26.4)	12 (3.1)

Neoplasm benign, malignant and unspecified	46 (12.0)	5 (1.3)	43 (11.2)	3 (0.8)
Nervous system disorders	128 (33.4)	26 (6.8)	87 (22.7)	13 (3.4)
Psychiatric disorders	49 (12.8)	2 (0.5)	34 (8.9)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	98 (25.6)	21 (5.5)	81 (21.1)	28 (7.3)
Skin and subcutaneous tissue disorders	132 (34.5)	16 (4.2)	197 (51.4)	69 (18.0)
Vascular disorders	58 (15.1)	11 (2.9)	28 (7.3)	8 (2.1)

Common drug-related treatment-emergent AEs – VFL plus CAPE

Treatment arm	VFL + CAPE (N = 383) N (%)		CAPE (N = 383) N (%)	
	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
Blood and lymphatic system disorders	89 (22.2)	54 (14.1)	46 (12.0)	21 (5.5)
Gastrointestinal disorders	240 (62.7)	49 (12.8)	178 (46.5)	29 (7.6)
General disorders and administration site conditions	182 (47.5)	32 (8.4)	87 (22.7)	12 (3.1)
Infections and infestations	28 (7.3)	5 (1.3)	16 (4.2)	1 (0.3)
Investigations	41 (10.7)	3 (0.8)	35 (9.1)	0
Metabolism and nutrition disorders	46 (12.0)	9 (2.3)	31 (8.1)	8 (2.1)
Musculoskeletal and connective tissue disorders	75 (19.6)	8 (2.1)	15 (3.9)	0
Nervous system disorders	67 (17.5)	8 (2.1)	31 (8.1)	2 (0.5)
Skin and subcutaneous tissue disorders	121 (31.6)	16 (4.2)	194 (50.7)	69 (18.0)
Vascular disorders	19 (5.0)	4 (1.0)	7 (1.8)	3 (0.8)

Adverse Events of Special Interest

Overview of drug-related treatment emergent AEs of special interest - Study VFL 305

Treatment arms	VFL + CAPE		CAPE	
No of patients (%)	383 (%)		383 (%)	
NCI CTC version 3.0 grading	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
Febrile neutropenia	8 (2.1)	8 (2.1)	2 (0.5)	2 (0.5)
Infection with severe neutropenia	3 (0.8)	1 (0.3)	0	0
Constipation	98 (25.6)	12 (3.1)	10 (2.6)	1 (0.3)
Ileus	3 (0.8)	2 (0.5)	0	0
Intestinal obstruction	6 (1.6)	5 (1.3)	0	0
Abdominal pain	124 (32.4)	18 (4.7)	57 (14.9)	4 (1.0)
Nausea	104 (27.2)	3 (0.8)	80 (20.9)	6 (1.6)
Vomiting	82 (21.4)	7 (1.8)	44 (11.5)	6 (1.6)
Stomatitis or mucositis	83 (21.7)	9 (2.3)	41 (10.7)	4 (1.0)
Diarrhoea	71 (18.5)	10 (2.6)	97 (25.3)	18 (4.7)
Myocardial infarction / ischaemia	2 (0.5)	1 (0.3)	0	0
Cardiac arrhythmias	3 (0.8)	1 (0.3)	1 (0.3)	0
Cardiac conduction disorders	0	0	0	0
Local injection/infusion site reactions	56 (14.6)	3 (0.8)	0	0
Extravasation	0	0	0	0
Peripheral sensory neuropathy	34 (8.9)	4 (1.0)	15 (3.9)	1 (0.3)
Peripheral motor neuropathy	2 (0.5)	0	0 1 (0.3)	0
Asthenia/Fatigue	128 (33.4)	25 (6.5)	77 (20.1)	11 (2.9)
Myalgia	28 (7.3)	3 (0.8)	4 (1.0)	0
Immediate hypersensitivity	4 (1.0)	0	2 (0.5)	1 (0.3)
SIADH	0	0	0	0
Hepatic dysfunction	0	0	0	0

PRES	0	0	0	0
Hand-foot syndrome*	89 (23.2)	14 (3.7)	180 (47.0)	69 (18.0)
* Grading by using Xeloda Summary of Product Characteristics. Of note, grade 4 is note applicable.				

Serious adverse event / deaths / other significant events

Serious adverse events (SAEs)
There were more patients with a SAE in VFL+CAPE arm (26.9% vs 21.7%) with twice as many related SAEs (13.3% vs 6%).
Serious adverse events (any grade)

Treatment arm	VFL + CAPE n=383	CAPE n=383
Total No of patients with at least one SAE	103 (26.9)	83 (21.7)
Total No of patients with at least one drug-related SAEs (suspected SAE are considered as drug-related)	51 (13.3)	23 (6.0)
No of patients with 1 drug-related SAE (%)	32 (8.4)	16 (4.2)
No of patients with 2 drug-related SAE (%)	10 (2.6)	4 (1.0)
No of patients with 3 drug-related SAE (%)	6 (1.6)	2 (0.5)
Blood and lymphatic system disorders	14 (3.7%)	6 (1.6%)
Cardiac disorders	1 (0.3)	1 (0.3)
Gastrointestinal disorders	31 (8.1%)	7 (1.8%)
General disorders and administration site conditions	7 (1.8%)	1 (0.3%)
Hepatobiliary disorders	1 (0.3)	2 (0.5)
Immune system disorders	-	1 (0.3)
Infections and infestations	5 (1.3%)	2 (1%)
Investigations	-	2 (0.5)
Metabolism and nutrition disorders	3 (0.8)	2 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.3)	-
Respiratory, thoracic and mediastinal disorders	-	1 (0.3)
Skin and subcutaneous tissue disorders	-	1 (0.3)
Vascular disorders	2 (0.5)	1 (0.3)

Deaths
At the cut-off date of 20th December 2011 (date for primary analysis), 232 patients in VFL+CAPE arm and 235 CAPE arm were dead. The main reason of death was progression in both arms (57.3% in VFL+CAPE arm and 56.0% in CAPE arm). For deaths within 30 days of the last study drug dose, the majority of deaths were due to disease progression, 5.5% of patients treated with VFL+CAPE and 5.7% of the CAPE arm. Two deaths (0.5%) in the VFL+CAPE arm were considered secondary to a drug-related AE and one (0.3%) in the CAPE arm.

Deaths within 30 days of the last study drug dose

	VFL + CAPE	CAPE
No of patients	384	383
No deaths < 30 days (%)	26 (6.8)	32 (8.4)
Deaths due to progression (%)	21 (5.5)	22 (5.7)
Deaths due to other reasons than progression (%)	3 (0.5)	9 (2.3)
Deaths due to drug-related AEs	2 (0.5) One Patient Febrile neutropenia Cycle 1 Day 8 One Patient Febrile	1 (0.3) One Patient Diarrhoea Cycle 1 Day4 (suspected dehydropyrimidine dehydrogenase deficiency)

	neutropenia Cycle 1 Day 12	
Deaths within 30 days after the last administration for reasons other than drug-related AEs or progression-VFL plus CAPE - Most probable cause of death		
Non drug-related AEs or not progression related	N=3 Cerebrovascular accident Sudden death Condition aggravated	N=11 Condition aggravated Condition aggravated Sudden death Hydrocephalus Cerebrovascular accident Dyspnoea Sudden death Death Multiple organ failure Sepsis Death

Laboratory findings

Clinical chemistry & hepatotoxicity Laboratory Abnormalities

Increases of bilirubin were seen in 19.1% of patients in the VFL+CAPE arm and 36.8% of patients in the CAPE arm. Increases in alkaline phosphatase were similar in each arm. Increases of AST were seen in 67.0% of patients in the VFL + CAPE arm and 58.4% of patients in the CAPE arm and ALT were seen in 54.3% of patients in the VFL + CAPE arm and 44.8% of patients in the CAPE arm.

- For serum creatinine analysis, similar grades were seen between arms
- Any grade of hyponatraemia 29.3% in the VFL + CAPE arm vs. 23.2% in the CAPE arm
- Any grade of hypokalaemia 18.6% in the VFL + CAPE arm vs. 24.5% in the CAPE arm
- Any grade of hyperkalaemia 12.8% in the VFL + CAPE arm vs. 7.7% in the CAPE arm
- No relevant clinical abnormalities were observed for calcaemia

Haematology

- Anaemia was more frequently reported in the VFL+CAPE arm (85.4% of patients) than in the CAPE arm (68.6%).
- Leucopenia was more frequently reported in the VFL+CAPE arm (64.1% of patients) than in the CAPE arm (44.7%). Grade 3 - 4 events were 16.4% vs. 4.3%.
- Neutropenia was more frequently reported in the VFL+CAPE arm (62.7% of patients) than in the CAPE arm (36.7%). Grade 3 - 4 events were 27.2% vs. 6.6%.
- Thrombocytopenia was more common in the CAPE arm (36.4%) vs VFL+CAPE arm (28.8%), though more grade 3-4 events were observed in the VFL+CAPE arm (3.4% vs. 1.1)

Safety in special populations

No new studies have been submitted.

Dose recommendation for special groups:

Hepatic impairment

Recommendations for VFL dose adjustment in monotherapy are provided in the SmPC.

No precise information is available for capecitabine in this specific population. In study VFL 305, patients were required to have total bilirubin < 1.5 x Upper Limit of Normal (ULN), transaminases < 2.5 x ULN or < 5 x ULN in case of liver metastases and alkaline phosphatase < 5 x ULN at study entry with no dose adjustment.

Renal impairment

The recommendations for dose adjustment of VFL monotherapy are provided in the SmPC.

The capecitabine dose of 825 mg/m² BID used in combination with vinflunine in study VFL 305 did not require dose adjustment in patients with the 30 ml/min < CrCl < 50 ml/min. In study VFL 305, creatinine clearance had to be at least 50 mL/min at study entry with no dose adjustment.

Elderly patients

The dose of vinflunine used in study VFL 305 which recruited patients less than 80 years old is consistent with the SmPC. For capecitabine, no dose adjustment is needed in elderly patients.

Discontinuation due to AEs

Discontinuation

Seventy one patients were discontinued from treatment because of an adverse event, whatever the relationship to the drug(s). Among these 71 patients, 52 (27 in arm A and 25 in arm B) were discontinued because of 56 drug-related AEs. The main reason for treatment discontinuation was disease progression in both study arms. Other reasons responsible for treatment discontinuation included patient's decision (11.2% in the VFL+CAPE arm, 4.9% in the CAPE arm).

Dose delays

A treatment cycle was considered as delayed if administered more than 3 days after the planned date (i.e. 3 weeks interval from day 1 of the previous cycle).When VFL is used in combination, with CAPE, the percent of dose delay was 38.6%. The reason for dose delay was mostly related to haematological AEs (42.2% of delayed cycles).

- 18.8% of patients had 1 cycle delayed
- 8.4% of patients had 2 cycle delayed
- 11.5% of patients had ≥3 cycle delayed

The most frequent reasons reported for cycle delay were haematological toxicities, mainly neutropenia in VFL+CAPE and non-haematological toxicities in the CAPE arm, the most common being palmar-plantar erythrodysesthesia (PPE) and hyperbilirubinemia.

Dose reductions

A total of 50 patients in the VFL+CAPE arm had at least one dose reduction of vinflunine. Dose reductions from 320 mg/m² to 280 mg/m² and from 280 mg/m² to 250 mg/m² were to be applied in case of haematological and/or non haematological toxicities. For the VFL+CAPE arm:

- 13.1% of patients had at least one dose reduction
- 1.3% of patients had at least two dose reductions

The most frequent reasons for vinflunine dose reduction were neutropenia (16.7% of all dose reductions), febrile neutropenia (13.3%) and constipation and intestinal obstruction (16.7%) for non-haematological toxicities.

73 patients in the VFL+CAPE arm A and 129 patients from the CAPE arm had at least one dose reduction of capecitabine. The most frequent reason for capecitabine dose reduction in both arms was drug related non-haematological toxicity. Hand and foot syndrome was the most frequent non-haematological toxicity that led to dose reduction.

Treatment-emergent AEs leading to treatment discontinuation

	VFL + CAPE n= 354		CAPE n=368	
Withdrawal due to AE (%)	35 (9.9)		36 (9.8)	
Withdrawal due to drug-related AE (%)	27 (7.6)		25 (6.8)	
Withdrawal due to non drug-related AE (%)	8 (2.3)		11 (3.0)	
	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
Blood and lymphatic system disorders	10 (2.8%)	9 (2.5)	6 (1.6)	4 (1.1)
Cardiac disorders	1 (0.3%)	1 (0.3)	-	-
Gastrointestinal disorders	5 (1.4%)	4 (1.1)	7 (1.9)	2 (0.5)
General disorders and administration site conditions	4 (1.1%)	2 (0.6)	3 (0.8)	1 (0.3)
Hepatobiliary disorders	2 (0.6%)	1 (0.3)	1 (0.3)	1 (0.3)
Investigations	1 (0.3%)	0	2 (0.5)	0
Metabolism and nutrition disorders	-	-	1 (0.3)	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.6%)	2 (0.6)	-	-

Nervous system disorders	3 (0.8%)	1 (0.3)	-	-
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1 (0.3)	-	-
Skin and subcutaneous tissue disorders	5 (1.4%)	2 (0.6)	8 (2.2)	5 (1.4)

Post-marketing experience

The first MA for Javlor was obtained on 21st September 2009 in European Union. More recently additional MAs have been obtained in Argentina, Lebanon, Australia, New-Zealand, Algeria, Morocco, Brazil, Singapore, Israel, Syria and Russia.

Javlor is currently marketed in accordance with marketing authorisation in Argentina, Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Lebanon, Netherlands, Norway, Poland, Spain, Sweden, United Kingdom, Luxembourg, Romania, Slovakia, Brazil, Morocco and Syria. A Named Patient Basis program is ongoing in Bahrain, Egypt and Emirates. In Switzerland, which does not have any MA for Javlor, physicians and hospitals are allowed to import Javlor from the EU zone.

The number of patients exposed is an estimation, since the first MA, the amount of Javlor sold worldwide was 12028.8 g corresponding to 7371 patients.

Post-marketing experience is issued from the Periodic Safety Update Reports which covered the period from 21 September 2009 to 21 September 2012, the last one covering the period from 22 September 2011 to 21 September 2012. Population exposed presented with transitional cell carcinoma of the urothelium (TCCU), except 1 patient treated for renal cancer (off-label use).

Since the first MA on 21 September 2009, 222 related case reports including 615 individual ADRs were registered in the Pierre Fabre pharmacovigilance database. Major SOCs involved were the following: “General disorders and administration site conditions” (53 case reports, 130 ADRs), “Blood and lymphatic system disorders” (45 case reports, 121 ADRs) and “Gastrointestinal disorders” (44 case reports, 121 ADRs).

Based on clinical safety data, important identified risks were defined as myelosuppression (including infection in a context of neutropenia), constipation / ileus and neurotoxicity. Important potential risks were ischaemic cardiac events, medication errors.

In addition to the important risks which emerged during pre-authorisation phase, new risks have been implemented during post-authorisation phase. The identified and potential risks for Javlor are listed below:

- Important identified risks:
    - Myelosuppression
    - Constipation and ileus
    - Neurotoxicity
    - Ischaemic cardiac events
    - Torsade de pointes/QT prolongation
    - Posterior Reversible Encephalopathy Syndrome PRES

- Important potential risks:
    - Medication errors
    - Off label use
    - Overexposure due to concomitant CYP3A inhibitor
    - Underexposure due to concomitant CYP3A inducer
    - Reproductive toxicity

2.5.2. Discussion on clinical safety

Patient exposure is considered to be sufficient for determining safety for the claimed indication, combining two known active medicinal products. 383 patients in the VFL+CAPE arm and 383 in CAPE arm received at least one dose of the study treatment (any of the study drugs in the combination arm). The median number of cycles per treated patient was 6.0 in the VFL+CAPE arm and 5.0 in the CAPE arm.

In terms of the incidence of adverse events, more VFL+CAPE patients compare to only CAPE arm patients experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation. As expected, the toxicity profile is more favourable in the CAPE arm. In general, treatment emergent adverse events (regardless of relationship) were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particularly blood and lymphatic system disorders (any grade, 24.5% vs 12.8%), gastrointestinal events (66.8% vs. 57.4%), general disorders and administration site conditions (63.7% vs. 43.3%), musculoskeletal and connective tissue disorders (39.2% vs. 26.4%) and nervous system disorders (33.4% vs. 22.7%). As expected, related treatment emergent adverse events were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particularly blood and lymphatic system disorders (any grade, 22.2% vs 12.0%), gastrointestinal events (62.7% vs. 46.5%), general disorders and administration site conditions (47.5% vs. 22.7%), musculoskeletal and connective tissue disorders (19.6% vs. 3.9%), nervous system disorders (17.5% vs. 8.1%) and vascular disorders (5% vs. 1.8%). Drug-related treatment emergent AEs of special interest were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particular, neutropenia, constipation, abdominal pain, nausea, vomiting, stomatitis or mucositis, local injection / infusion site reactions, peripheral sensory neuropathy, asthenia/Fatigue and myalgia.

More drug-related SAE were experienced in the VFL+CAPE arm compared to the CAPE arm, in particular gastrointestinal disorders (8.1% vs. 1.8%) and blood and lymphatic system disorders (3.7 vs. 1.6). The most frequent SAEs in patients treated with VFL+CAPE were constipation (2.1% of patients) and febrile neutropenia (1.8%). At the cut-off date of 20th December 2011 (date for primary analysis), 232 patients in VFL+CAPE arm and 235 CAPE arm were dead. For deaths within 30 days of the last study drug dose, the majority of deaths were due to disease progression, 5.5% of patients treated with VFL+CAPE and 5.7% of the CAPE arm. Two deaths (0.5%) in the VFL+CAPE arm were considered secondary to a drug-related AE and one (0.3%) in the CAPE arm.

Patient's decision was a more common reason for discontinuation in the VFL+CAPE arm (11.2%) versus the CAPE arm (4.9%). The reason for patients' decision for ending study treatment is not known from this study.

2.5.3. Conclusions on clinical safety

More VFL+CAPE patients compare to only CAPE arm experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation.

2.6. Risk management Plan

The PRAC considered that the risk management plan version 14 is acceptable. The PRAC endorsed assessment report is attached.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The addition of vinflunine to capecitabine reduced the risk of progression or death by 16%. Median PFS was 4.3 months in the CAPE arm and 5.6 months in the VFL+CAPE arm, median difference 1.3 months (HR 0.84 95% CI : 0.71 - 0.99, P = 0.0426). Only a favourable trend toward an increased median OS was observed, median OS was 13.9 months in the VFL+CAPE arm and 11.7 months in the CAPE arm, difference 2.2 months (HR 0.98, 95% 0.83 - 1.15, P = 0.7657). Objective response rate (CR + PR) assessed by IRC showed a slight trend in favour of the VFL+CAPE arm (22.9% vs. 17.9%) and the disease control rate (CR + PR + SD) was 57.3% in the VFL+CAPE arm compared to 47.9% in the CAPE arm. A continuous improvement in the global health status score was observed for the VFL+CAPE arm.

Uncertainty in the knowledge about the beneficial effects

The proposed new indication is supported by a single pivotal study. The results from VFL 305 are not considered to be statistically compelling for the purposes of a marketing authorisation application supported by a single study. No effect on other important secondary endpoints has been shown.

Risks

Unfavourable effects

In terms of the incidence of adverse events, more VFL+CAPE patients experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation. As expected, related treatment emergent adverse events were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm; blood and lymphatic system disorders (any grade, 22.2% vs 12.0%), gastrointestinal events (62.7% vs. 46.5%), general disorders and administration site conditions (47.5% vs. 22.7%), musculoskeletal and connective tissue disorders (19.6% vs. 3.9%), nervous system disorders (17.5% vs. 8.1%) and vascular disorders (5% vs. 1.8%). Drug-related treatment emergent AEs of special interest were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE

only arm. In particular, neutropenia, constipation, abdominal pain, nausea, vomiting, stomatitis or mucositis, Local injection / infusion site reactions, peripheral sensory neuropathy, asthenia/fatigue and myalgia.

Uncertainty in the knowledge about the unfavourable effects

Patient decision was a more common reason for discontinuation in the VFL+CAPE arm (11.2%) versus the CAPE arm (4.9%). The reason for more discontinuations is not known.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Importance of favourable effects

The claimed magnitude of effect on the primary endpoint PFS is small and supported by only positive trends in other important secondary endpoints.

Importance of unfavourable effects

The tolerability of the combination therapy can be questioned. More VFL+CAPE patients compare to only CAPE arm experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation.

Benefit-risk balance

The additional toxicity profile burden is not outweighed by the potential for small benefits in PFS, therefore the indication is not approvable.

Discussion on the Benefit-Risk Balance

The effect on PFS is modest and no effect on overall survival or other important secondary endpoint has been shown. This does not outweigh the additional toxicity observed. Therefore, the benefit risk balance is considered to be negative for the claimed indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication: in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve, previously treated with or resistant to an anthracycline

and who are taxane resistant.

Grounds for refusal

Whereas

- The efficacy of vinflunine in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve previously treated with or resistant to an anthracycline and who are taxane resistant has not been demonstrated due to a modest improvement in PFS being observed;
- Patient exposure is considered to be sufficient and shows an additional toxicity profile burden of the combination of vinflunine with capecitabine compared to the capecitabine only treated patients in the claimed indication;
- In the absence of established efficacy and considering the additional toxicity of the combination treatment, the benefit-risk balance is considered negative;

the CHMP on the grounds of Article 16 of Regulation 1234/2008/EC has recommended the refusal of the variation to the terms of the Marketing Authorisation.

Additional data / Market exclusivity

Considering the refusal of the proposed indication, the applicant's claim that this therapeutic indication brings significant clinical benefit in comparison with existing therapies pursuant to Article 14(11) of Regulation (EC) No 726/2004 is unfounded.