European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Javlor

International Nonproprietary Name: vinflunine ditartrate

Procedure No. EMEA/H/C/000983

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Pierre Fabre Médicament submitted on 6 February 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Javlor, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 1 June 2007.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: Javlor is indicated in monotherapy for the treatment of patients with advanced or metastatic transitional cell carcinoma of urothetial tract after failure of a prior platinum-containing regimen.

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Ian Hudson** Co-Rapporteur: **Gonzalo Calvo Rojas**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 6 February 2008.
- The procedure started on 27 February 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 May 2008.
- During the meeting on 23-26 June 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2008.
- A clarification meeting with the Rapporteurs on the CHMP List of Questions was held on 26 August 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 December 2008
- During the CHMP meeting on 15-18 December 2008 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 23 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 6 April 2009.
- During a SAG Oncology on 8 April 2009, experts were convened to address questions raised by the CHMP .

- Following the SAG Oncology meeting, the applicant submitted further responses to the CHMP members on 15 April 2009.
- During the CHMP meeting on 20-23 April 2009 the CHMP agreed on a second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP second list of outstanding issues on 25 April 2009.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 11 May 2009.
- During the CHMP meeting on 26-29 May 2009 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The applicant submitted further responses to the CHMP following the oral explanation on 3 June and 8 June 2009.
- The Rapporteurs circulated a further updated Joint Assessment Report on the applicant's responses following the oral explanation to all CHMP members on 10 June 2009.
- During the meeting on 22-25 June 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Javlor on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2009.

2 SCIENTIFIC DISCUSSION

3.1 Introduction

Transitional cell carcinoma urothelium (TCCU)

TCCU comprises of bladder cancer (90%), renal pelvis (9%) and ureteral carcinoma (1%). Radical cystectomy is the recommended treatment in most cases of infiltrating, non-metastatic bladder carcinoma. External beam irradiation, with elective salvage cystectomy for residual local recurrence is preferred in some centres. Despite standard treatment, up to 30-40% of patients will develop distant metastases and approximately 15% of patients will be found to have regional or distant metastasis at diagnosis. Metastatic TCCU represents an aggressive disease that is associated with a median survival that rarely exceeds 3 - 6 months if left untreated.

Transitional cell carcinoma of the urothelium is considered to be a chemosensitive tumour. However, chemotherapy confers only a modest survival benefit and metastatic disease remains essentially incurable, with only a small number of patients achieving long-term disease control. Both Performance Status (PS) and visceral involvement are prognostic factors predictive of overall survival after 1st line treatment of patients with metastatic TCCU. A number of chemotherapeutic agents have single agent activity against urothelial cancer, achieving mainly partial responses of short duration. Combination therapy may yield response rates of 30-35%. M-VAC (methotrexate + vinblastine + doxorubicin + cisplatin combination) or GC (gemcitabine + cisplatin) are regimens for metastatic TCCU.

There is currently no standard therapy in patients with advanced urothelial carcinoma, whose disease has progressed after or during a prior platinum-containing regimen. These patients have a median survival of approximately 4 months and a poor prognosis. No randomised studies have been conducted in this patient group for single agent treatment of second line TCCU. Phase II studies have been conducted in small populations of patients (< 60) that show response rates ranging from 0% with bortezomib to 29% with gemcitabine.

The Medicinal Product

Javlor 25 mg/ml concentrate for solution for infusion belongs to the pharmacotherapeutic group of *Vinca* alkaloids and analogues, ATC code: L01CA05. 1 ml of concentrate contains 25 mg of vinflunine (as ditartrate). Vinflunine (Javlor) is a microtubule inhibitor. Microtubules are involved in the maintenance of cell shape, mobility, adhesion and intracellular integrity as well as having a role in

the formation of the mitotic spindle during proliferation. 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 arrestand apoptosis. *In vivo* vinflunine displays a significant antitumor activity against a broad spectrum of human xenografts in mice both in terms of survival prolongation and tumour growth inhibition.In common with other Vinca agents, vinflunine blocks cells at the G2/M phase of the cell cycle and induces cell death via 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. The efficacy and safety of vinflunine has not been studied in patients with a Performance Status ≥ 2. Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy. Before each cycle, adequate monitoring of complete blood counts should be conducted to verify the absolute neutrophil counts (ANC) as neutopenia is a frequent adverse reaction of vinflunine.

The recommended posology is 320 mg/m² as a 20-minute intravenous infusion every 3 weeks. In case of WHO/ECOG Performance Status (PS) of 1 or of 0 and prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m². In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

3.2 Quality aspects

Introduction

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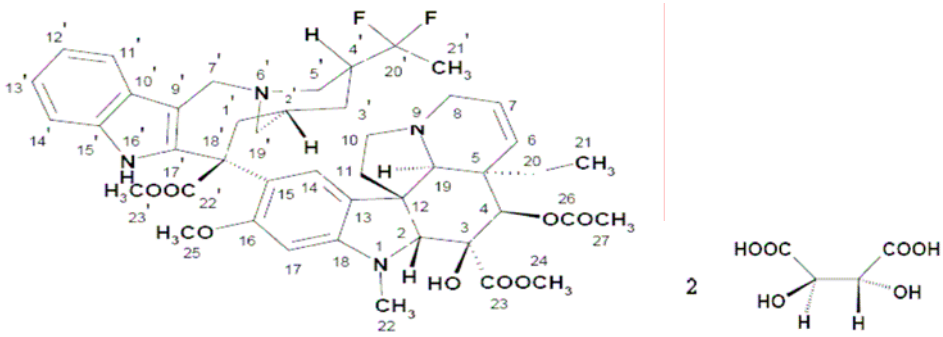
Javlor is concentrate for solution for infusion and contains 25 mg/ml of vinflunine base as active substance (corresponding to 34.175 mg/ml of vinflunine ditartate). The finished product is available in 50 mg/2 ml, 100 mg/4 ml and 250 mg/10 ml single-use vials. The container closure system is a type I colourless glass vial with a chlorobutyl or a laminated butyl rubber stopper and an aluminium flip-off seal.
The other ingredients are water for injections and nitrogen (low oxygen).

Javlor is diluted with a suitable parenteral fluid, sodium chloride 0.9 % solution or glucose 5% solution to obtain a solution ranging from 3 mg/ml to 7 mg/ml prior to intravenous infusion. Compatible admixture fluids and administration sets have been qualified and use-times and storage conditions for diluted solutions for infusion have been established.

Active Substance

Its chemical name is ((2β,3β,4β,5α,12*R*,19α)-4-(acetyloxy)-6,7-didehydro-15-[(2*R*,4*R*,6*S*,8*S*)-4-(1,1-difluoroethyl)-1,3,4,5,6,7,8,9-octahydro-8-(methoxycarbonyl)-2,6-methano-2-Hazecino[4,3-b]indol-8-yl]-3-hydroxy-16-methoxy-1-methyl-aspidospermidine-3-carboxylic acid methyl ester, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:2).



Vinflunine ditartate is white to off-white powder, very hygroscopic and it is an amorphous substance. It is freely soluble in water, soluble in ethanol and practically insoluble in dichloromethane. It is important to underline that this active substance has a strong buffering power.
The active substance has 9 chiral centres and its absolute stereochemical configuration was established. In this context, the active substance will be used as single enantiomer (2R, 3S, 4R, 5R, 12R, 19R, 2'S, 4'R, 18'S).

- **Manufacture**

Vinflunine ditartate is synthesised in nine reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by filtration and then undergoes lyophilisation allowing the isolation of the dried active substance.
Structure elucidation has been performed by elemental analysis, mass spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, ^{19}F-NMR spectroscopy, ultraviolet spectroscopy, infrared absorption spectroscopy and circular dichroïsm.
The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight. The proposed molecular structure was confirmed by single crystal X-ray diffraction and the absolute stereochemistry was confirmed with data from NMR spectroscopy and circular dichroïsm.

- **Specification**

Vinflunine ditartate specifications include tests for appearance (white to off-white powder), solubility, Identification (IR, HPLC, TLC, Identification of tartrates), appearance of solution S (Ph.Eur), pH of solution S (Ph.Eur), absorbance of solution S (Ph.Eur), water content (Ph.Eur), sulphated ash (Ph.Eur), tartaric acid content (Ph.Eur), assay residual solvents (Ph.Eur), impurities (Ph.Eur) and microbiological limit tests (Ph.Eur).
All specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were carried out according to the general methods described in the Ph.Eur.
Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results of 26 batches comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term (-20°C ± 3°C) and accelerated studies (5 °C ± 3°C) were completed according to ICH guidelines demonstrated adequate stability of the active substance. During the stability studies the following parameters were controlled: appearance (white to off-white powder), appearance of solution S (Ph.Eur), pH of solution S (Ph.Eur), absorbance of solution S (Ph.Eur), water content (Ph.Eur), tartaric acid content (Ph.Eur), impurities, microbial contamination,

assay and LC assay. It was noticed that the test methods applied are those used for release of the drug substance with exception of LC assay. All the validation parameters have been submitted for this analytical method (LC assay). It was confirmed that the active substance remained within the specifications for up to 48 months after long term storage at -20°C. Moreover, no major unexpected changes were observed in the active substance after storage under accelerated stress studies, which were performed under heat, humidity, light, oxidation conditions and in solutions with different pH. Following the results from stress studies it was concluded that the active substance was sensitive to temperature, humidity and oxidation.
The photosability study that was performed in accordance with the note for guidance on photostability testing of new active substances and medicinal products (CPMP/ICH/279/95) confirmed that the active substance is photosensitive.
Based on the stability results it was concluded that the active substance can be stored 48 months protected from light in the proposed container closure system at a temperature at or below -15°C before being retested.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified.
The main objective was to develop a stable, sterile, aqueous solution of vinflunine ditartrate for intravenous administration. Based on the properties of the active substance an aqueous solution was selected for development.
The concentration, which was used during the clinical trials, was changed to 25mg/ml in order to adapt the formulae to the recommended dose in human and reduce wastage of the medicinal product, which is not used. The final formulation contains the active substance at a concentration of 25 mg/ml expressed as vinflunine base. The vehicle of this pharmaceutical form is water for injections and an inert gas (nitrogen low oxygen), which is used to protect the oxidation of the active substance. Good stability has been shown in unbuffered aqueous solution. Adjustment of the isotonicity of the finished product is not necessary since the administration is done by infusion after dilution in sodium chloride 0.9 % solution or glucose 5% solution. Taking into account that Javlor is presented in single-use vials, which have been sterilised, no antimicrobial preservatives have been used
Compatibility studies show that the finished product is stable with the proposed rubber stoppers and that there is no container-content incompatibility between the product diluted in sodium chloride 0.9% or glucose 5% solution at a concentration range between 3 mg/ml and 7 mg/ml and polyvinylchloride bag or polyethylene bag. This is accepted. The container closure system integrity is demonstrated by sampling 50 vials from the media fill test for each presentation vials and the results show negative microbial growth for all samples tested.

- **Manufacture of the Product**

This Manufacturing process consists of the following steps: mixing, sterilisation, filling and packaging. The vials are washed and sterilised by dry heat; stoppers and flip-off seals are steam sterilised using a validated cycle. The critical steps of this particular manufacturing process have been identified.
Satisfactory process validation data have been provided for the major steps of the manufacturing process. All process validation batches are of maximum production scale size and all data are within specifications.
The in process controls are adequate for this pharmaceutical form. The batch analysis results show that the medicinal product can be manufactured reproducibly according to the agreed finished product specifications.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance, particulate contamination (Ph.Eur), identification (LC and UV), extractable volume (Ph.Eur), absorbance value at 420 nm (Ph.Eur), bacterial endotoxins (Ph.Eur), related substances (LC), impurities (LC) and assay (Ph.Eur). It was noted that the impurity limits in the specification are justified by toxicology studies
All relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Stability of the Product**

The stability results from long-term (5°C ± 3°C) and accelerated studies (25 °C 60% RH) were completed according to ICH guidelines demonstrated adequate stability of the finished product. All stress studies, which were preformed under stressing conditions (40 °C 75% RH), low temperatures, cold chain failure conditions, artificial lightning (photostability studies in accordance with the note for guidance on photostability testing - CPMP/ICH/279/95), have been performed, which are the extreme dosages. It was noticed that a detail justification for performing bracketing has been provided.
Based on the results of the available stability data it can be concluded that the finished product must be protected from light. However, it was demonstrated that it can be exposed directly to ambient lighting not more than 1 day at room temperature. Javlor can undergo 1 or 2 freeze-thaw cycles from a freezing temperature between -15°C and -25°C to a thawing between +2°C and + 8°C. It was verified that the authorised cold chain failure is limited to 14 days up to +30°C protected from light. Furthermore, it was demonstrated that Javlor diluted at 3 to 7 mg of the active substance per ml of sodium chloride 0.9 % or glucose 5 % solution can be stored: in a polyethylene or polyvinylchloride bag for 1 day at room temperature protected from light, 6 days in the refrigerator (+2°C and + 8°C) protected from light or in a polyethylene or polyvinylchloride infusion set for 1 hour at room temperature (25°C) exposed to ambient lighting. From a microbiological point of view, the finished product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Finally it can be concluded that the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. At the time of the CHMP opinion, there was an unresolved quality issue, which will not have an impact on the benefit/risk ratio of the medicinal product. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3.3 Non-clinical aspects

Introduction

The non-clinical development programme of vinflunine consisted of pharmacology studies (primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology), pharmacokinetic studies, toxicology studies (single dose toxicity, repeat dose toxicity, genotoxicity, reproductive and developmental toxicity, and local tolerance studies) and an environmental risk assessment.

Pharmacology

- Primary pharmacodynamics

In vitro studies showed that VFL inhibits tubulin polymerisation, induces mitotic arrest and apoptotic cell death. These studies demonstrated that along with other microtubule inhibitors, tubulin was a common intracellular target. VFL appears to suppress the rate and extent of microtubule growth and also suppresses microtubule treadmilling, but with a weaker potency than the other Vinca alkaloids. Microtubule treadmilling is necessary for normal chromosome progression through mitosis, so these data suggest that VFL might have subtly different effects from the other Vinca alkaloids on certain mitotic events.

Antitumour activity was identified in three other murine 'solid' tumour models, the orthotopically-implanted MB-49 bladder tumour and the MAC15A and MAC29 transplantable colon adenocarcinomas. Definite activity (defined by optimal T/C ranging from >135 to 179%) was reported with VFL against the sc-implanted M109 lung carcinoma using various multidose schedules. Overall antitumour activity with VFL was documented in five of the seven murine 'solid' tumours tested.

A summary of the *in vitro* studies conducted is represented in the table below.

Table 1: In vitro pharmacology studies with Vinflunine

Description	Results
In vitro sensitivity of L1210 murine lymphocytic leukaemia cells to VFL	VFL induced a concentration-dependent inhibition of L1210 murine leukaemia cell growth, with a dose-response curve suggestive of a narrow dose-range of cytotoxicity.
Modulation by verapamil of the in vitro drug-induced cytotoxicity of VFL on the P388 sensitive murine leukaemia cell line, a doxorubicin resistant subline	Using this method, after a 48-hour drug exposure, the IC50 value obtained was 72 nM. Comparable results were obtained to the previous study (L0070-17492)
Differential in vitro cytotoxic effects of the compound F12158 against a panel of solid tumour cell lines quantitated by colourimetic metabolic dye-based MTT assay	VFL resulted in a similar pattern of cytotoxicity, versus the nine tumour cell lines to that of vinblastine and vinorelbine. The response induced by VFL was dose-dependent, showing a plateau-shaped cytotoxic dose effect, observed with other tubulin-interacting agents.
Flow cytometric studies of in vitro cell cycle modification induced by vinblastine, vinorebline or VFL in the P388 murine Leukaemia cell line and doxorubicine-resistant P388/ADR subline	Flow cytometric analyses of cellular DNA content by propidium iodide staining of P388 leukaemia cells exposed to VFL showed an accumulation of cells in the G2+M phases of the cell cycle
Effects of F 12158 on murine L1210 leukaemia cell division in vitro	Exposure to VFL resulted in an accumulation of these cells in mitosis and that the proportion of these mitotic cells within the total population increased with increasing concentrations of VFL.
Effects of F 12158 on the interphase microtublar cytoskeletion of a rat aortic smooth muscle cell line, A-10, *in vitro*: an anti-tubulin immunoflurescence study	VFL induced a concentration-dependent reduction of the microtubular network of interphase cells, with complete loss occurring at 1 µM. At higher levels (> 10 µM), VFL caused aggregation of microtubules with the formation of paracrystals.
Effects of F 12158 on the proteolysis of purified tubulin with chymotrypsin or trypsin/ Effects of VFL on the GTPase activity of purified tubulin	VFL induced an increase of proteolysis by chymotrypsin, without the appearance of a new proteolytic band known to form in the presence of bound colchicine and podophyllotoxin. VFL also inhibited proteoloysis by trypsin, an effect noted in the presence of bound *Vinca* alkaloids. The binding of VFL to tubulin appears to induce structural changes in tubulin consistent with its interaction at or near the *Vinca* binding domain
Characterisation of the effects of F 12158 on the binding of 3H-vinorelbine or 3H-colchicine to tubulin	VFL did not appear to inhibit significantly the binding of either tritiated colchicine or -vinorelbine to unpolymerised tubulin *in vitro.* When comparing the capacity of unlabeled *Vinca* alkaloids to VFL to inhibit the binding of 3H-vinorelbine to tubulin, the compounds tested could be classified (in terms of their competitive efficiencies, tubulin-binding affinities) as vincristine> vinblasine> VFL.
***In vitro* uptake of titrated VFL or**	Accumulation of VFL was higher than that of

titrated vinorelbine by P388 sensitive murine leukaemia cells and a doxorubicine-resistant P388/ADR subline	vincristine and vinblastine by 560% and 280% respectively, under comparable experimental conditions. However, uptake and efflux characteristics of VFL and vinorelbine were essentially identical.
Drug induced cytotoxicity of a series of tubulin-interacting agents against sensitive and resistant murine (P388) and human (CEM; MCF&: T24: GLC4) tumour cell lines *in vitro/* Drug induced cytotoxicity of VFL against sensitive and resistant murine (P388) and human (CEM; MCF&: T24: GLC4) tumour cell lines *in vitro*	Neither subline showed any resistance to VFL. There was some collateral sensitivity to VFL in the teniposide-resistant line. No resistance was noted in these cell lines for vinblastine or vinorebine either. In contrast, definite cross-resistance to VFL was expressed by three classic MDR Pgp-overexpressing cell lines.
Flow cytometric studies of in vitro cell cycle modifications induced by vinblastine, vinorelbine or VFL in the P388 murine leukaemia cell line and doxorubicin-resistant P388/ADR subline Modulation by verapamil of the in vitro drug induced cytotoxicity of VFL on P388 sensitive P388 murine leukaemia cell line and doxorubicin-resistant subline	VFL induced a dose-dependent arrest in the G2+M phases of the cell cycle.
uptake of titrated VFL or tritiated vinorelbine by P388 sensitive murine leukaemia cell line and doxorubicin-resistant subline P388/ADr subline/ uptake of titrated VFL by P388 sensitive murine leukaemia cell line and doxorubicin-resistant subline P388/ADr subline	VFL proved a less potent inducer of resistance than vinorelbine, as quantified by drug sensitivity estimations.

In vivo studies

Data from human tumour xenografts (applying strict application of NCI toxicity criteria), showed definite significant activity in two melanomas, one lung and one renal tumour, whilst moderate activity was noted in one pleura mesothelioma. (See table below),

Xenograft Tumour (type)	No. of Expts.	Tumour Inhibitory Activities of Vinflunine applying	
		Fiebig's criteria	NCI criteria
GXF97 (stomach)	3	Active	All expts.unevaluable – major toxicity & lethalities
GXF209 (stomach)	3	Inactive	Inactive-2 expts & toxicity 1 expt.
MEXF276 (melanoma)	3	Active	Active – 2 expts & toxicity 1 expt.
MEXF989 (melanoma)	2	Active	Active – 1 expt & toxicity 1 expt
PAXF737 (pancreatic)	2	Active	All expts. unevaluable – major toxicities
PAXF1657 (pancreatic)	2	Active	All expts. unevaluable – major toxicities
LXFA629 (lung)	3	Active	Active
LXFA289 (lung)	1	Inactive	Inactive from single experiment
LXFA529 (lung)	2	Inactive	Inactive
RXF1220 (renal)	3	Active	Active – 2 expts & lethalities in 1 experiment
RXF486 (renal)	1	Inactive	Inactive from single experiment
PXF537(pleuramesothelioma)	2	Active	Active
PXF541(pleuramesothelioma)	1	Inactive	Inactive from single experiment
OVXF899 (ovarian)	2	Inactive	Inactive - 1 expt & toxicity 1 expt
OVXF1023 (ovarian)	3	Inactive	All expts.unevaluable – major toxicities
A2780 (ovarian)	3	Inactive	Inactive - 2 expts & toxicity in 1 experiment

The data show that the in vivo activity of VFL against both murine and human tumour experimental models was achieved at considerably higher doses than those of vinorelbine. Activity of VFL was achieved in the absence of any significant body weight loss (i.e. ≤ 15%) or early deaths, in tumour-bearing animals.

- Secondary pharmacodynamics

Studies addressing secondary pharmacodynamics have not been submitted.

- Safety pharmacology programme

The safety pharmacology programme is summarized in the table below.

Table 3. Safety pharmacology programme of Vinflunine

	Description	Results
Central Nervous System	**Irwin behaviour test in mice**	At 50 mg/kg, hypothermia was noted at 15, 30 and 60 minutes after treatment. At 25 mg/kg, a reduction in body temperature was noted at 15 and 30 minutes after treatment. However, an increase in body temperature at 12.5 and 25 mg/kg, 24 hours after dosing was also noted. No other effects were noted. The no-effect dose was considered to be 6.25 mg/kg.
	Study of spontaneous activity in mice locomotor activity	VFL induced a dose-related decrease in spontaneous locomotor activity (-7.0 % to -66.5 %) during the first and second 10-min observation periods, as well as during the 30-min period.
Cardiovascular	**Cardiac action potential in isolated canine Purkinje fibres**	VFL at a concentration of 10^{-4} M induced decreases in action potential duration, in particular APD50. Decreases in the plateau of action potential (APD50) and in maximal rate of depolarization, suggesting possible inhibition of calcium and/or sodium currents, were noted.
	hERG	VFL inhibited hERG current by 12.9% (n = 3), 37.7 % (n = 3) and 70.1% (n = 3) at 3, 10 and 30µM, respectively. The calculated IC50 was 15.0 µM.
	Evaluation of cardiovascular effects of intravenous VFL ditartrate on anaesthetized dogs	The primary ECG effect was a dose-related change in T wave morphology and amplitude in some animals: 1/5 at 3 mg/kg, 2/5 at 6 mg/kg and 3/5 at 9 mg/kg. These morphology and amplitude changes returned to the baseline values 180 minutes after dosing. At 9 mg/kg, transient effects were noted on cardiovascular parameters but not on arterial blood gases. At 3 and 6 mg/kg, no significant effects on cardiovascular and arterial blood gases parameters were noted.
	Electrocardiographic evaluation of VFL ditartrate intravenously on anaesthetized dogs	No significant changes in PQ, QRS, QT, and QTc intervals, heart rate, blood gases and blood biochemical parameters, were noted. However, the amplitude and morphology of the T-wave was altered.
	Evaluation of coronary effects of VFL ditartrate following intravenous administration in the anaesthetized dog	No significant effects on PQ, QRS, QT and QTc, T wave amplitude, left ventricular end diastolic pressure, heart rate and blood gases (pH, pO2, pCO2) or rectal temperature were found.
	Evaluation of effects of VFL ditartrate on blood pressure, heart rate and electrocardiogram after single intravenous dosing in conscious dog	No statistically significant effect on mean, systolic and diastolic arterial pressures over the 48-hour post-dosing period was noted. A statistically significant sinus tachycardia was seen from approximately 6 hours to 36 hours after dosing.
	Cardiovascular and respiratory effects VFL ditartrate in the anaesthetized Cynomolgus monkey following intravenous administration	The main effects seen in this study were a decrease in heart rate accompanied by an increase in RR interval and an increase in T wave amplitude. Heart rate decreased from a baseline mean of 156 bpm to 135 bpm and showed partial recovery to 145 bpm, 120 min after administration, but had not completely recovered by 240 minutes
Respiratory	**Effect of VFL on respiration in the unrestrained conscious mouse following single intravenous administration**	No statistically significant changes in respiratory parameters were noted at 20 mg/kg. At 40 and 60 mg/kg, a dose-dependent decrease in respiratory rate (- 38 to 41%), increases in inspiration (+ 44 to 48%), and expiration times (82 to 90%) and an increase in tidal volume (+ 55 to 59%) were seen. These effects were associated with a decrease in airway resistance at 60 mg/kg.
	Evaluation of respiratory effects of VFL intravenously on anaesthetized dogs	VFL administered intravenously had no important effects on respiratory and arterial blood gases parameters or rectal temperature in this study
Haematological effects	**Evaluation of haemolytic activity of VFL**	VFL ditartrate at 1.4 x 10^{-4} M sensitized rabbit erythrocytes to the lytic action of hypotonic sodium chloride solutions. No haemolytic effects were evident at concentrations up to 4.2 x 10^{-5} M.
	Evaluation of the effect of VFL ditartrate on platelet aggregation induced by collagen and arachidonic	At a concentration of 10^{-4}M a statistically significant antiplatelet effect on platelet aggregation induced by collagen with a percentage of inhibition of 51 %. This effect was not statistically

	acid on rabbit platelets	significant at a concentration of 10^{-5M}
Renal	**Study of diuresis and urinary biochemistry of VFL ditartrate in the rat following single iv administration**	VFL exhibited no relevant effect on diuresis, urinary biochemistry, or creatinine clearance in the rat when compared to controls.
Gastrointestinal	**Ulcerogenic effects of a single iv dose of VFL ditartrate on the gastric mucosa in Sprague- Dawley rats**	VFL had no effect on the occurrence of hyperemia and ulcers in the gastric mucosa of the rat when compared with controls at any of the doses examined.
	Effects of a single iv dose of VFL ditartrate on gastric emptying and intestinal transit of a test meal in mice	At 12.5 or 25 mg/kg no effect on gastric emptying and intestinal transit in mice was noted. At 50 mg/kg, VFL significantly reduced gastric emptying (- 26 %) of the test meal, but did not effect intestinal transit.
	Effects of a single iv dose of VFL ditartrate on gastric secretion in pylorus-ligated rats	VFL had no effect on gastric secretion in pylorus-ligated rats at 0.67 or 2 mg/kg. At 6 mg/kg, VFL reduced the volume of gastric secretion and decreased total acidity, but did not affect the pH of gastric secretion, nor free and titratable acidity.
Interaction with morphine	**Interaction between morphine and VFL on the respiratory function in the conscious rabbit**	Doses of 3, 6 or 12 mg/kg VFL ditartrate did not modify arterial blood gases. It did not change the respiratory depressant effect induced by morphine given i.v, indicating that there is no interaction between morphine and VFL on respiratory function in this study.
	Study of the possible analgesic properties of a single intravenous dose of VFL in combination with a single intraperitoneal dose of morphine in the hot plate test in mice	At 12.5, 25 and 50 mg/kg, VFL increased the latency before pain appearance in a dose-dependent manner. This slight analgesic effect was not statistically significant

- Pharmacodynamic drug interactions

The affinity of VFL ditartrate for various receptors was assessed in radioligand binding assays. At a concentration of $1x10^{-5}$ M, 4-O deacetyl VFL did not cause any significant inhibition of specific radioligand binding at the receptors studied, which indicates that it is devoid of affinity for these receptors at this concentration. However, the study showed a micromolar affinity of VFL for opiate non selective receptors and μ receptors with a Ki value of 1120 nM. This was nearly 1000-fold higher than that of the reference agonist opioid peptide.

Pharmacokinetics

The iv route of administration was used exclusively for all studies described (mouse, rat ,dog, monkey). Rats and monkeys were the principal species selected for the safety evaluation of VFL. Additional pharmacokinetic studies were conducted using 4-O-deacetyl VFL (DVFL) to document the contribution of this active metabolite to the toxicological profile of VFL.

Single dose pharmacokinetic studies with blood and plasma samples, were performed with radiolabelled VFL ([3H]-VFL), while toxicokinetic studies were performed after both single or repeated doses with non-radiolabelled drugs.

Overall, (in all species) exposure (AUC) was dose-proportional and was generally linear. In all four species, the pharmacokinetics of VFL in blood was characterised by a decrease in concentration over the first hours post i.v. bolus followed by slower distribution and elimination phases. The elimination half-life of total radioactivity was close to 100 h while T½z of unchanged VFL varied from 4 to 20 hours. Tissue distribution was large (volume of distribution between 12 and 36 L/kg). No drug accumulation was noticed after repeated administrations over 26 weeks in monkeys whereas a trend to accumulation was suggested in rats after 4-week and 26-week administration. A high volume of distribution suggests extensive tissue uptake.

In vitro studies performed with human liver microsomes showed that VFL had neither inducing effects on CYP1A2, CYP2B6 or CYP3A4 activity nor inhibition effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (see SPC section 4.5).

In vitro pharmacodynamic studies showed that vinflunine is a Pgp-substrate as the other vinca alkaloids, but with a lower affinity. Therefore, risks of clinically significant interactions should be unlikely.

DVFL was found to be a major metabolite in man. DVFL was observed in blood, urine and faeces from all species. Single doses of DVFL were investigated in rats and monkeys (1 mg/kg in rats and 6 mg/kg in monkeys). Pharmacokinetics of DVFL was characterised by a slow distribution and elimination phase. The terminal elimination half-life was about 34 h and 45 h in rats and monkeys, respectively.

Toxicology

- Single dose toxicity

The results of the single dose toxicity studies are summarized in the table below.

Table 4: Single Dose Toxicity Studies with Vinflunine

Animal Model	Dose	Results
Mouse	60, 63, 65 and 80 mg/kg (180, 189, 195 and 240 mg/m^2).	The LD0 was considered to be ≤63 mg/kg and the LD10 was ≥65 mg/kg.
	60 mg/kg (180 mg/m^2)	The neutropaenia, lymphopaenia, and decreases in erythropoiesis that occurred at 60 mg/kg were severe 5 days after dosing and were in general reversible following a 1-month recovery period
	60, 65, 70 or 80 mg/kg (180, 195, 210 or 240 mg/m^2).	The LD0 was < 60 mg/kg (180 mg/m^2) for males and 60 mg/kg (180 mg/m^2) for females, and the LD10 was approximately 65 mg/kg (195 mg/m^2).
Rat	5, 7.5, 10, 15 or 22 mg/kg (30, 45, 60, 90 or 132 mg/m^2).	The LD0 was considered to be approximately 7.5 mg/kg (45 mg/m^2). The LD10 was between 7.5 mg/kg (45 mg/m^2) and 10 mg/kg (60 mg/m^2).
Dog	0.34, 0.50, 0.67, 1.01, 1.34, 1.68, 2.69, 4.48, 8.96 and 13.45 mg/kg; 6.8 to 269 mg/m^2)	At dose levels ≥8.96 mg/kg leukopaenia, neutropaenia, and anaemia indicative of bone-marrow toxicity were noted. Increases in ALT and ALP were indicative of liver toxicity. The MTD in dogs was considered to be 13.45 mg/kg.
	4, 6, 9 and 12 mg/kg (80, 120, 180 and 240 mg/m^2)	Test article-related findings included leukopaenia, neutropaenia, and anaemia at all doses and were considered attributable to bone-marrow toxicity; and the increases in liver enzymes at 9 and 12 mg/kg were considered attributable to liver toxicity. These changes were reversible at the 9 mg/kg, and the MTD was considered to be approximately 9 mg/kg (180 mg/m^2).
Cynomolgus monkey	4, 9, 12 and 16 mg/kg (48, 108, 144 and 192 mg/m^2)	Decreases in bone-marrow myelopoiesis was noted; this was attributed to bone-marrow toxicity. The MTD was considered to be approximately 16 mg/kg (192 mg/m^2).

Systemic single-dose exposures (24-hour area under the concentration-time curve [AUC0-24]) to VFL in dogs and monkeys were similar between males and females. Mean single-dose IV systemic VFL exposures in animals are summarized and compared to the AUC in humans at the recommended IV clinical dose of 320 mg/m^2 in the table below.

Table 5. Mean VFL Blood Exposures in Dogs and Monkeys vs Humans

Species	Study	Dose mg/kg (mg/m^2)	AUC_{0-24hr} (ng•h/mL)		Multiple of Human Exposure (x) Based on AUC_{0-24h} 320 mg/m^2	
Human	Q21D, i.v.	(320)	8783[a]		-	
			Males	Females	Males	Females
Dog	single-dose, i.v.	9 (180)	8346	7336	0.95	0.83
Monkey	single-dose, i.v.	16 (192)	18358	13628	2.09	1.55

a: dose-adjusted AUC0-24h from n=49 patients

- Repeat dose toxicity

Repeated-dose i.v. toxicity studies completed with VFL included a 5-day study in mice, pivotal 1-month studies in rats and monkeys, a 3-month study in rats and 6-month studies in rats and monkeys. Dosing in the rat and monkey studies was intermittent and occurred twice weekly. The main signs of toxicity in the subchronic and chronic toxicology studies of VFL are weight loss, haematological and clinical chemistry changes, mainly neutropaenia. These toxicities are expected based on the pharmacological effects of VFL and have been demonstrated to be either partially or completely reversible. The bone-marrow and liver were also target organs.

Table 6: Repeat-dose toxicity studies. Main findings

Study ID	Species	Dose (mg/kg)	Duration	NOAEL (mg/kg)	Major findings
IMT 435 GLP	Mouse (Swiss) 5/males/dose	13, 16, 20 and 30	5 days		- 100% mortality at 30 mg/kg
IMT 620 GLP	Rat (Sprague Dawley) 10/sex/dose	0.3; 0.6, 1.2, 3 and 6.4	2 x wk for 4 wk	0.6	- Leucopenia, Neutropenia, thrombocytopenia and decrease serum immunoglobulins at 3 and 6.4 mg/kg. - Bone marrow depletion at 6.4 mg/kg
IMT 677 GLP	Rat (Sprague Dawley) 15/sex/dose	0.3, 1.0 and 3.5	2 x wk for 13 wk + 4 wk recovery	0.3	- Leucopenia, neutropenia, thrombocytopenia (3.5 mg/kg) - Increase in ALT and AST (3.5 mg/kg) - Reversible decrease in relative liver weight (all doses) - Deaths at 3.5 mg/kg (6 males and 1 female)
IMT 730 GLP	Rat (Sprague Dawley) 25/sex/dose	0.3, 0.8 and 2.0	2 x wk for 26 wk + 4 wk recovery	0.3*	**All doses**: - Decrease in leukocyte, neutrophil, eosinophil, monocyte and lymphocyte - Increase in ALT, ALP and AST
* NOEL <0.3 but NOAEL = 0.3					
CIT 16805 GLP	Monkey (Cynomolgus) 4/sex/dose	1.0, 2.2 and 5.0	2 x wk for 4 wk	< 1	- Dose-related leukopenia and neutropenia - Anemia at 2.2 and 5 mg/kg - At 5 mg/kg thymic lymphoid depletion
CIT 17953 GLP	Monkey (Cynomolgus) 6/sex/dose	0.4, 1.3, 4.0 and 10.0	2 x wk for 26 wk + 4 wk recovery	1.3	-Swelling at injection site and soft faces. - 4 and 10 mg/kg reversible leukopenia, neutropenia, anemia and bone-marrow hypoplasia - 10 mg/kg death (2 females) and thymic lymphoid depletion

- Genotoxicity

The genotoxic potential of VFL was evaluated in a battery of *in vitro* and *in vivo* studies. VFL is positive in mutagenicity and genotoxicity assays. The table below summarizes the results of these studies.

Table 7: Genotoxicity Studies with Vinflunine

Study Number	Description	Results
L0070-FSR- IPL-040302	**Mutagenicity test on Salmonella typhimurium**	VFL was considered to be not mutagenic
L0070-IPL-R 980401	**Mutation assay at the TK locus in L5178Y mouse lymphoma cells**	VFL was mutagenic and clastogenic without metabolic activation in mammalian mouse lymphoma cells.
L0070-IPL-R 980408	**Mutagenicity study using the micronucleus test in rat**	VFL and vincristine were clastogenic in the rat micronucleus test. At equitoxic doses, the clastogenic activity of VFL was lower than that of vincristine

- Carcinogenicity

No carcinogenicity studies were submitted. The carcinogenic potential of VFL has not been studied according to ICH S1A and CPMP/SWP/99796.

- Reproduction Toxicity

Reproductive and developmental toxicity studies conducted with VFL (IV) include assessment of potential effects on fertility and reproductive function in male and female rats, evaluations of embryo-fetal development in rats and rabbits and effects on pre- and post-natal development in rats. Preliminary, dose range-finding studies in rats and rabbits were conducted to assist in dose selection for the pivotal reproductive toxicity studies. Exposure assessments were conducted in the rabbit embryo-fetal development study.

In the rat embryotoxicity and fetotoxicity were noted, characterized by increased number of dams with no viable fetuses, increased early resorptions, postimplantation loss and reduced fetal weights at higher doses. In the rabbit, higher doses of VFL were embryotoxic and teratogenic (malformations included cleft palates, exophthalmia, microtia, anotia, dome-shaped head, cranioschisis, misshapen head or vertebral bones, hemivertebrae, fused or divided ribs, and reduced ossification of head, vertebrae or talus). In the rat ppn study, maternal toxicity was evident in F0 generation dams. In addition, decrease in body weight gain and decreases in food consumption were seen in the undosed F1 adult females. At higher doses, malformations of the uterus and vagina and a reduced number of conceptuses were observed in F1 generation females.

A number of malformations were noted in the rat embryo toxicity study. These findings might be considered to indicative of teratogenicity. Therefore, both male and female patients should take adequate contraceptive measures up to three months after the discontinuation of the therapy. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine. (see section 4.6 of the SPC).

Due to the possible very harmful effects on the infants, breast-feeding during the treatment with vinflunine is contraindicated (see section 4.3 of the SPC).

- Toxicokinetic data

Toxicokinetic evaluations were conducted in rats and monkeys as part of the repeat dose *i.v.* toxicology studies with VFL. There were not gender differences neither drug accumulation based on AUC observed in the different studies (Tables 8 and 9).

Table 8: Vinflunine exposures in Rats vs. Humans

Species	Study	Dose mg/kg (mg/m^2)	AUC_{0-24hr} (ng•h/mL)Day 1		AUC_{0-24hr} (ng•h/mL) Last day		Multiple of Human Exposure Based on AUC 320 mg/m^2	
Human	Multiple dose (Q21D) i.v.	(320)	8783[d]		8783[d]		-	
			Males	Females	Males	Females	Males	Females
Rat	1 month, twice weekly i.v.[a]	0.3/6.4 (1.8/38.4)			343/4888	205/3643	0.04/0.56	0.02/0.41
		0.6 (3.6)	571	396	451	351	0.05	0.04
		1.2 (7.2)	1022	876	946	705	0.11	0.81
		3 (18)	2803	2236	1607	1723	0.18	0.20
Rat	3 month, twice weekly i.v.[b]	0.3 (1.8)	176	202	224	207	0.03	0.02
		1 (6)	711	705	741	634	0.08	0.07
		3.5 (21)	1979	2350	1943	2112	0.22	0.24
Rat	6 month, twice weekly i.v.[c]	0.3 (1.8)	110	203	280	228	0.03	0.03
		0.8 (4.8)	432	564	685	580	0.08	0.07
		2 (12)	876	1543	1579	1409	0.18	0.16

a – last day AUC values from Day 25 except at 0.3 mg/kg (Day 1); b – last day AUC values from Day 92; c – last day AUC values from Day 176 for 0.3 mg/kg and from Day 88 for 0.8 and 2 mg/kg. d: dose-adjusted AUC0-24h from n=49 patients [L0070 99 IN101 Q0, L0070 99 IN102 Q0]

Table 9: Vinflunine Exposures in Monkeys vs. Humans

Species	Study	Dose mg/kg (mg/m^2)	AUC_{0-24hr} (ng•h/mL) Day 1		AUC_{0-24H} (ng•h/mL) Last day		Multiple of Human Exposure Based on AUC 320 mg/m^2	
Human	Multiple dose i.v.	(320)	8783[f]		8783[f]			
			Males	Females	Males	Females	Males	Females
Monkey	1 month, twice weekly i.v.[a]	1 (12)	714	773.3	658	696	0.07	0.08
		2.2 (26.4)	1741.3	1581.7	1676	1473	0.19	0.17
		5 (60)	3745	4067.3	3338	3320	0.38	0.38
Monkey	6 months, twice weekly i.v.[b]	0.4 (4.8)	238[g]	231[g]	244	274	0.03	0.03
		1.3 (15.6)	819	837	874	7782477[c]	0.10	0.09
		4 (48)	2623	2477	2623[c]	7077[e]	0.30	0.28
		10 (120)	5999	6415	6232[d]		0.71	0.81

a – Last day AUC values from Day 30; **b** – Last day AUC values from Day 176; **c** – AUC values reported from Day 1, as AUC_{last} values reported from Day 85 and Day 176 are calculated from 0 to 48h; **d** - Due to mortality, AUC values from Day 85; **e** - Due to mortality, AUC values from Day 71; **f**: dose-adjusted AUC0-24h from n=49 patients ; **g**: AUC_{0-9h}

- Local tolerance

The table below summarizes the local tolerance studies submitted.

Table 10: Local Tolerance Studies with Vinflunine

Study Number	Description	Results
98-0186	***In vitro* study of the cytotoxicity of VFL and vinorelbine ditartrate on skin cells**	VFL and vinorelbine had no adverse effect on human epidermal cells at the concentrations studied
98-0216	**Evaluation of the ocular irritation potentially induced by VFL in the rabbit**	VFL without ocular rinsing was considered a slight irritant.
98-0179	**Local tolerance of VFL in the rabbit by intravenous, perivenous and intra-arterial route**	VFL was well tolerated after i.v. injection, but it induced vascular irritation when administered perivascularly or intraarterially at a concentration of 2 mg/mL
06-0269	**Acute dermal irritation/corrosion in rabbits**	25 mg/mL VFL was an irritant, in particular on abraded skin, but was not a vesicant.

- Other toxicity studies

The table below summarizes additional toxicity studies submitted. The major human metabolite of VFL and the only one active is 4-O-deacetyl VFL (DVFL). DVFL was tested in a battery of nonclinical toxicity studies listed below**.** The non-clinical safety of VFL impurities was also evaluated in several studies listed below.

Table 11: Additional Toxicity Studies with VFL/DVFL/VFL impurities

Study Description	Results
***In vitro* haematotoxicity of VFL ditartrate - comparison to vinorelbine ditartrate, vincristine sulfate and paclitaxel**	VFL was less toxic *in vitro* to bone-marrow progenitor cells than vinorelbine, paclitaxel and vincristine
***In vitro* thrombocytopoietic toxicity of VFL - comparison to vinorelbine, vincristine and paclitaxel**	VFL, vincristine and paclitaxel were equally toxic to bone-marrow progenitor cells, whereas vinorelbine was more toxic than these compounds.
Evaluation of peripheral nervous system safety pharmacology - effects of VFL on rat dorsal route ganglion neurons	At concentrations ≤ 0.01 µg/mL, VFL had no neurotoxic effects on DRG neurons; whereas vincristine and vinorelbine were toxic at all concentrations. In this in vitro model, the neurotoxicity of VFL was lower than that of vincristine and vinorelbine.
Four week toxicity study by the intravenous route in rat - VFL vs DVFL	The toxicity of DVFL was considered to be limited to the irritant properties of this type of compound at the site of administration and did not appear to contribute to the toxicity of VFL.
Four week toxicity study by twice weekly intravenous injection (bolus) in cynomolgus Monkey	The toxicity profile of DVFL is similar to that of VFL when equivalent exposures are achieved
5-day toxicity study by the intravenous route in rats followed by a 2-week recovery period	Haematological, biochemical and microscopic changes were similar across the batches tested. The toxicity profile was comparable for the 4 batches of VFL tested in this study
5 -day toxicity study by the intravenous route in rats followed by a 2-week recovery period	The toxicity profile for the two batches of VFL tested in this study were comparable: reference batch 515 and batch 515 spiked with 23-O-demethylVFL and 6'-N-oxyVFL impurities (respective relative individual content of 1.09 and 1.91 %).
5-day toxicity study by the intravenous route in rats followed by a 2-week recovery period	Apart from increases in urinary clearance and/or concentration recorded in the batch 501 only for urea, sodium, potassium and chloride at 5 mg/kg/day, the toxicity profile is comparable for the 2 batches of VFL tested in this study: reference batch 517 and batch 501 spiked with 5 impurities

Four-week toxicity study by the intravenous route in male rat – VFL vs stressed VFL	The toxicity profile for the two batches were similar
Neutral red uptake phototoxicity assay in Balb/c 3T3 mouse fibroblasts	VFL values were 0.010 and 0.027 in 2 trials, indicating that VFL is not phototoxic to 3T3 cells.

- Impurities/Metabolites

With identified impurities (Δ-7,8-VFL-3,6-ether (D8), 6'-N-methylVFL (D7), 23-O-demethyl VFL, Nor-7'-VFL (D2), 6'-N-OxyVFL (D11), 7', 16'- didehydroVFL (RRT 1.4) Ames assays on 4 strains (TA 1537, 98, 100 and 102) were carried out, along with in vitro micronucleus tests on mouse lymphoma cells. A summary of the results is found in the table below.

Table 12: Impurities of Vinflunine, Summary of Study Results

Impurity	**Ames TA 1537, 98, 100, 102 (micromethods)**	**Study Number**	**L5178Y Micronucleus S9+ /S9- (micromethods)**	**Study Number**
Δ-7,8-vinflunine-3,6-ether (D8)	Negative	FSR-IPL 040015	Less genotoxic than VFL	FSR-IPL 040013
6'-N-methylvinflunine (D7)	Negative	040016	Less genotoxic than VFL	040024
23-O-demethylvinflunine	Negative	040017	Less genotoxic than VFL	040025
Nor-7'-vinflunine (D2)	Negative	050209	Less genotoxic than VFL*	050210
6'-N-oxyvinflunine (D11)	Negative	060201	Less genotoxic than VFL	060202
7', 16'- didehydrovinflunine (RRT 1.4)	Negative	041003	Less genotoxic than VFL	041004

*After 24 hour continuous treatment, if the incidence of the number of micronuclei was higher for D2, a significant genotoxic activity was observed at lower concentrations for VFL

Ecotoxicity/environmental risk assessment

The applicant submitted an ERA. The Log Kow for vinflunine was below 4.5. The calculation of PECsw using this Fpen and a maximum daily dose of 320 mg/m2 would be equal to 0.000726 µg/L, i.e. a value far below the threshold of concern for environment, that is 0.01 µg/L .

Discussion on the non-clinical aspects

The CHMP considered that the applicant had conducted an extensive programme of pharmacology studies, indicating that VFL has a relevant pharmacodynamic effect. The applicant also conducted adequate safety pharmacology and pharmacokinetics programmes. Rats and monkeys were the principal species selected for the safety evaluation of VFL. A small number of pharmacokinetic studies were conducted using 4-O-deacetyl VFL (DVFL) to document the contribution of this active metabolite to the toxicological profile of VFL. The single-dose studies were adequate and no further studies were required. The intravenous infusion studies provided sufficient information on toxicity at higher doses. The duration of repeat-dose studies was also considered adequate and the absence of carcinogenicity studies was adequately justified. An acceptable programme of genotoxicity studies was conducted. VFL is positive in mutagenicity and genotoxicity assays. Given the pharmacology of the compound and the proposed indication, this was considered acceptable. The carcinogenic potential of VFL was not studied, according to ICH S1A or CPMP/SWP/99796. In the reproductive toxicity studies performed, embryotoxicity and fetotoxicity were noted.

During the evaluation of the non-clinical data submitted as part of this dossier, the following concerns were identified.

1. The applicant was requested to modify the wording of section 4.4 and 5.3 of the SPC regarding the cardiac safety of vinflunine. The safety margins provided from the Purkinje assay along with no adverse cardiac events in the monkey up to 16 mg/kg, provided some reassurance regarding vinflunine's potential to alter ventricular repolarization, however given that there were other test article-related cardiovascular findings in some other non-clinical studies and agents that disrupt normal microtubules function have shown to affect essential cardiac activities, the statement in section 5.3 of the SPC (''Vinflunine did not induce peripheral neuropathy nor cardiotoxicity in animals'') was modified to delete the reference to cardiotoxicity. Section 4.4 of the SPC was also amended to include a statement for the management of patients with prior history of myocardial infarction/ischemia or angina pectoris.

2. A number of malformations that may be considered indicative of developmental toxicity (teratogenicity) were noted in the pregnant rat. In addition, malformed fetuses from 2 litters containing 1 or 2 viable fetuses were noted. The resorption rate in these litters was high, possibly suggesting that this finding might have been due to possible malformations in the resorbed fetuses. Malformations of the uterus and vagina (2 females has closed vaginas) were noted in the rabbit; these were not reported in the rat. The applicant was therefore asked to discuss further information on the precise nature of the skeletal observations noted, whether the malformations are considered species specific, and to address their clinical relevance. In response to this concern, Section 4.6 and 5.3 of the SPC were amended as follows.

SPC Section 4.6 Pregnancy:
There is no data available about the use of vinflunine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3). On the basis of the results of animal studies and the pharmacological action of the product, there is a potential risk of embryonic and foetal abnormalities.
Vinflunine should therefore not be used during pregnancy, unless it is strictly necessary. If pregnancy occurs during treatment, the patient should be informed about the risk for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy.

SPC Section 5.3 Preclinical safety data:
In the reproduction studies, vinflunine appeared to be embryolethal and teratogenic in rabbits and teratogenic in rats. During the pre- and post-natal development study in rat, vinflunine induced malformations of the uterus and vagina in 2 females, and adversely affected mating and/or ovule implantation and markedly lowered the number of *concepti.*

Section 4.3 of the SPC reflects the following:

Hypersensitivity to the active substance, other vinca alkaloids.
Recent (within 2 weeks) or current severe infection.
Baseline ANC < 1,500/mm^3 or platelets < 100,000/mm^3
Lactation (see section 4.6)

3.4 Clinical aspects

Introduction

The clinical development programme of vinflunine consisted of pharmacokinetic studies (distribution, excretion, metabolism, dose proportionality, special populations, drug-drug interactions and safety/interaction studies), pharmacodynamic studies, and main clinical studies.

The clinical development program for solid malignancies included the following studies as a single agent:
-5 completed Phase I studies
-4 ongoing Phase I studies
-10 completed Phase II studies (variety of tumour types including melanoma, metastatic renal cell carcinoma, malignant pleural mesothelioma, advanced ovarian cancer)
-1 completed Phase III study (NSCLC)
-1 ongoing Phase II study (metastatic breast)
-1 Phase II study in gastric cancer (premature termination)

Studies in combination therapy were:
- 4 completed Phase I/II studies
- 4 ongoing Phase I/II studies
- 1 Phase I/II (early termination)
- 1 ongoing Phase III study, in HER2 negative metastatic breast cancer
- 1 Phase III study in first line treatment of TCCU

For the proposed indication, the clinical program for vinflunine in second-line treatment in patients with TCCU after platinum-containing chemotherapy regimens includes:

- 3 phase I trials (VFL 981, VFL 991, VFL 992)
- 2 phase II studies (VFL202, CA 001)
- 1 randomised Phase III study (VFL 302)

GCP

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

The applicant 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.

Pharmacokinetics

The clinical pharmacokinetics were evaluated in cancer patients. The tumours of the patients who participated in the phase I/II clinical trials included all types of solid cancer, such as bladder cancer (Urothelial Transitional Cell Carcinoma of Urothelium, TCCU), non-small cell lung cancer (NSCLC) and breast cancer.

Vinflunine pharmacokinetics is linear in the range of administered doses (from 30 mg/m² to 400 mg/m2) in cancer patients.
Blood exposure to vinflunine (AUC), significantly correlated with severity of leucopenia, neutropenia and fatigue.

The clinical pharmacology studies with Vinflunine are listed below:

Table 13. Clinical Phase I studies with Vinflunine single agent

Study Number	Objective(s)	Study design	Test product(s): dosage regimen	Number of PK evaluable patients	Diagnosis of patients	Study status
9 L0070 98 IN 101 Q0 See 2.7.6, see file	PK and determination of MTD	Open label, dose escalating	VFL doses ranging between 30 and 400 mg/m², q3w	30	Advanced solid tumours	Completed
9 L0070 99 IN 101 Q0 See 2.7.6, see file	PK and determination of MTD	Open label, dose escalating	VFL doses ranging between 120 and 250 mg/m² weekly	34	Advanced solid tumours	Completed
9 L0070 99 IN 102 Q0 See 2.7.6, see file	PK and determination of MTD	Open label, dose escalating	VFL doses ranging between 170 and 210 mg/m² VFL on Days 1 and 8, q3w	15	Advanced solid tumours	Completed
9 L0070 99 IN 103 Q0 See 2.7.6, see file	PK, metabolism, excretion, safety	Open label, single dose	Tritiated VFL dose of 250 mg/m²	5	Solid tumours	Completed
L00070 IN 1 04 Q0 See 2.7.6, see file	PK and safety in liver-impaired patients	Open label, dose escalating	VFL at dose of 320 mg/m² or lower q3w, depending on toxicities observed	25	Various solid tumours and liver impairment	Completed
L00070 IN 1 13 Q0 See 2.7.6, see file	PK and safety in renal-impaired patients	Open label, dose escalating	VFL at 280 mg/m² q3w if modest renal impairment; at 250 mg/m² q3w if severe; possible dose escalation to 320 mg/m²	22	Various solid tumours and renal impairment	Ongoing
L00070 IN P US 101 Q0 / CA 183009 See 2.7.6, see file	PK and safety of VFL given alone and with ketoconazole	Open-label, sequential, 2-cycle, 2-treatment study	Cycle 1: VFL 80 mg/m² on Day 1 and oral ketoconazole 400 mg on Days –1 through 7; VFL dose escalation to 160, 240 and 320 mg/m² based on safety. Cycle 2: VFL 320 mg/m² on Day 1 q3w	10	Advanced solid tumours	Ongoing

Table 14. Phase II studies with Vinflunine single agent Phase II and combined chemotherapies Phase I trials

Study Number	Objective(s)	Study design	Test product(s): dosage regimen	Number of PK evaluable patients	Diagnosis of patients
Phase II studies of VFL as single agent: completed studies					
L00070 IN P US 202 G0 / CA183001 See 2.7.6, see file	Primary – to assess RR. Secondary – to assess duration of response; TTR; disease control rate; PFS; overall survival; safety	Phase II, open-label, single-arm study of VFL as second-line therapy	VFL at 320 or 280 mg/m² q3w	31	Advanced or metastatic TCC of the urothelium after failure on a platinum-containing regimen
L00070 IN 206 B0 See 2.7.6, see file	Primary – to assess RR Secondary – to assess DR; PFS; OS; safety and PK	Phase II, open-label, single-arm study of 2nd-line VFL therapy	VFL at 320 mg/m² q3w	19	MBC after failure of anthracycline-taxane therapy
L00070 IN 207 B0 See 2.7.6, see file	Primary – to assess RR Secondary – to assess DR; PFS; OS; safety and PK	Phase II, open-label, single-arm study of 3rd-lineVFL therapy	VFL at 320 mg/m² q3w	11	MBC after failure of anthracycline-taxane therapy
L00070 IN 208 E2 See 2.7.6, see file	Primary – to assess RR Secondary – to assess duration of response; PFS; OS; safety and PK	Phase II, open-label, single-arm study of 2nd-line VFL therapy	VFL at 320 mg/m² q3w	8	Advanced ovarian cancer after platinum of taxane failure
L00070 IN 209 J1 See 2.7.6, see file	Primary – to assess RR Secondary – to assess duration of response; PFS; OS; safety and PK	Phase II, open-label, single-arm study of 2nd-line VFL therapy	VFL at 320 mg/m² q3w	12	Advanced NSCLC after failure of platinum-containing regimen
L00070 IN 210 J3 See 2.7.6, see file	Primary – to assess RR Secondary – to assess PFS; OS; safety and PK	Phase II, open-label, single-arm study of 1st-line VFL therapy	VFL at 320 mg/m² q3w	13	First line for malignant pleural mesothelioma
Study Number	**Objective(s)**	**Study design**	**Test product(s): dosage regimen**	**Number of PK evaluable patients**	**Diagnosis of patients**
Studies of VFL in combination with other agents: completed studies					
L00070 IN 105 J1 See 2.7.6, see file	Primary – to determine RD of VFL + cisplatin, followed by response rate of VFL + CDDP Secondary – to assess safety; PK and efficacy of combination	Phase I/II, open-label study of 1st-line VFL	VFL at 250, 280 or 320 mg/m² + 80 mg/m² of cisplatin, q3w	41	Advanced NSCLC
L00070 IN 107 J1 See 2.7.6, see file	Primary – to determine RD of VFL + carboplatin Secondary – to assess safety; PK and efficacy of combination	Phase I, open-label study of 1st-line VFL	VFL 280 mg/m² + carbo AUC5, VFL 320 mg/m² + carbo AUC5, or VFL 320 mg/m² + carbo AUC6 q3w	21	Advanced NSCLC
L00070 IN 108 J1 See 2.7.6, see file	Primary – to determine the RD of pegylated liposomal doxorubicin hydrochloride (PLDH) Secondary – toxicity; PK; PK relationship to safety and activity of combination	Phase I, open-label	VFL 250 or 280 mg/m² + PLDH at 20 or 25 mg/m², both q3w VFL 150 mg/m² + PLDH 20 or 25 mg/m² q3w VFL 170 mg/m² + PLDH 25 mg/m² q3w	40	Advanced solid tumors

- Methods

Two types of bioanalytical methods were used to quantify VFL and its metabolites in human biological samples:

- **Methods dealing with radiolabelled detection and measurement,** used to explore the *in vitro* plasma proteins and blood cells binding and the *in vitro* and *in vivo* metabolism of VFL (Study L0070 99 IN103 Q0). These methods consisted of liquid scintillation counting of β particles emitted by tritium from ^{3}H-VFL and ^{3}H-metabolites. HPLC methods were generally used for controls.

- **Methods for non-radiolabelled detection,** used to quantize of unchanged VFL and its metabolites in biological fluids.

  HPLC/UV: The HPLC/UV technique was the method employed in most of the clinical studies, in order to measure VFL and 4-O-deacetylvinflunine (DVFL) in blood and VFL in urine. In blood, the method is linear from 2-200 ng/mL with a lower limit of quantification (LLOQ) at 2 ng/mL (coefficient of variation (CV) < 7%) and in urine, from 20 and 2000 ng/mL with LLOQ at 20 ng/mL (CV < (3%). The intraday and interday precision and accuracy values were evaluated on 6 replicates of quality control (QC) samples processed over 3 days and they were within usual acceptance limits of QC samples for daily run (15% at each concentration level: low, middle, and high).
  Most of the bioanalyses were performed in a single laboratory however a few ones (studies L00070 IN108 J1, L00070 IN110 B0, L00070 IN111 B0, L00070 IN208 E2 and L00070 IN210 J3) were completed in another facilityA cross-validation of the HPLC method was performed comparing the results from the two laboratories and before analysis of the biological samples obtained from the concerned studies. The mean bias between the two laboratories was 6.3% for VFL and 13.7% for DVFL. The individual deviations of 8 out of 10 samples were within the acceptability limits (*i.e.* ≤ ± 15%). VFL and DVFL chemical stability in stored samples from clinical trials was demonstrated to be sufficient for easy routine use of the bioanalytical methods.

  LC/MS-MS: A HPLC method followed by tandem mass spectrometry detection. This method was used for metabolites identification from human biological samples (blood, urine and faeces) by ATC laboratories (Study M821 and Study 20968) and for assessing the mass-balance distribution of VFL and its metabolites after ^{3}H-VFL administration (Study 9 L0070 99 IN 103 Q0). In addition, it was used for evaluating in vivo the potential PK drug-drug interaction (DDI) with ketoconazole (Study CA183009).

  The method was linear over the range: 0.25-1.000 ng/mL for VFL en blood, 0.25-200 ng/mL for DVFL in blood, 20- 5000 ng/mL in urine and 2-1000 µg/g in faeces for both compounds. The intraday and interday precision (CV %) calculated on QC samples were less than 6.9% and 15.9% for VFL and 7.1% and 5.2% for DVFL in blood while the accuracy (mean bias, %) was lower than 9.1% and 7.1% for VFL and DVFL, respectively. In urine and faeces, the precision (CV %) was lower than 5.6% in urine and 8.2% in faeces. The accuracy (mean bias, %) was lower than 7% in both media for both compounds.

Both HPLC/UV and LC/MS-MS methods were developed and validated according to GLP.

- Absorption

No absorption studies were submitted.

- Distribution

Vinflunine is moderately bound to human plasma proteins (67.2±1.1%) with a ratio between plasma and whole blood concentrations of 0.80±0.12. Protein binding mainly involves high density lipoproteins and serum albumin and is non-saturable on the range of vinflunine concentrations

observed in patients. Binding to alpha-1 acid glycoprotein and to platelets is negligible (< 5%). The terminal volume of distribution is large, 2422±676 litres (about 35 l/kg) suggesting extensive distribution into tissues.

- Elimination

The PK of vinflunine and its metabolites were studied after a 15-min infusion of 3H-VFL at a single dose of 250 mg/m². Blood samples were collected over 7 days, while urine and faeces were collected over 14 days. Total radioactivity in blood, urine and faeces was measured by liquid scintillation counting (LSC) and vinflunine and metabolites were quantified according to LC/MS-MS method.

The table below summarizes the population PK parameters obtained.

Table 15: Vinflunine clearance in blood and variabilities

	Pool of early Phase I data studies	**First population PK model** *(Study IRPF L00070-20127)*	**Global PK population study** *(Study IRPF 22284)*	
		No covariate	**No covariate**	**With covariates (BSA, Cl_{creat} and PLDH)**
Nb of patients	79	59	372	
Nb of PK datasets	79 (1st administration only)	151 (from 1st to 4th administrations)	656 (from the 1st to 4th administrations)	
Method of estimation	Model-dependent Bayesian approach	Non Linear Mixed Effect approach	Non Linear Mixed Effect approach	
Mean VFL Cl_{tot}	42.3 L/h	39.1 L/h	39.7 L/h	**40.5 L/h**
Inter-patient variability (CV%)	24%	25%	28%	**25%**
Intra-patient variability (CV%)	n.c.	11%	8.6 %	**8.3%**

n.c.: not calculated.

The metabolism of vinflunine was examined in both *in vitro* and *in vivo* studies. From *in vitro* studies (hepatic microsomes, hepatocytes cultures, insect transfected cells). A total of 11 metabolites are detected in blood, urine and faeces.

7 metabolites were directly formed from vinflunine in one step reaction:

- DVFL (M1 – the only active metabolite); VFL 3,6 ether (M2); desmethyl-VFL (M4); VFL 6'-oxide (M9); 2 isomers of hydroxy-VFL (M3, M6/7) and one unidentified structure named 815d (M13)

Sequential metabolism is presumed for 4 other structures:

- Di-hydroxy-VFL (M10), desmethyl-VFL 3,6 ether (M15), desmethyl-815d (M16) and hydroxy VFL 3,6 ether (M18)

Major metabolites were:

- DVFL (M1), VFL 3,6 ether (M2), desmethyl VFL (M4) and VFL 6'-oxide (M9). All other metabolites were either minor or detected at trace levels

Vinflunine is eliminated following a multi-exponential concentration decay, with a terminal half-life (t ½) close to 40 h. DVFL is slowly formed and more slowly eliminated than vinflunine (t ½of approximately 120 h).The excretion of vinflunine and its metabolites occurs through faeces (2/3) and urine (1/3). In a population pharmacokinetic analysis in 372 patients (656 pharmacokinetic profiles),

the total blood clearance was 40 l/h with low inter and intra-individual variability (25% and 8%, respectively, expressed as coefficient of variation).

All metabolites identified are formed by the cytochrome CYP3A4 isoenzyme, except for 4Odeacetylvinflunine (DVFL), the only active metabolite and main metabolite in blood which is formed by multiple esterases. The characterisation of human cytochrome P450 isoenzymes involved in vinflunine metabolism shows that other isoenzymes studied were either not or weakly involved (CYP1A2, CYP2D6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 were not involved). DVFL was not generated by CYP but formed through multiple esterases. The metabolic pathway of vinflunine involves both the nor 7' velbanamine and vindoline parts of the molecule. All structures went through phase I reactions. Phase II enzymes are not involved in vinflunine metabolism. No conjugated metabolite was observed.

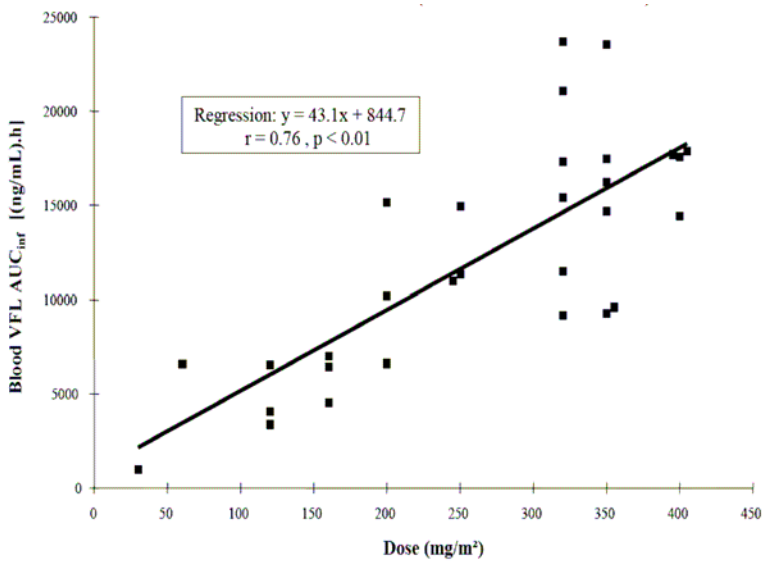
- Dose proportionality and time dependencies

A phase I and PK study of vinflunine given as a 10-minute infusion every 3 weeks was carried out to explore the PK profile of vinflunine. Ten dose levels of vinflunine from 30 mg/m² up to 400 mg/m² were administered and PK assessment was performed in 30 patients.

Vinflunine blood concentrations vs. time profiles were characterized by a sharp concentration decrease over the first 30 minutes following the end of infusion and then demonstrated a slower distribution /elimination phase (data not shown).

The mean VFL total clearance was high (Cltot = 41.4 ± 12.9 L/h or 0.63 ± 0.23 L/h/kg) and its inter-individual variability (calculated by coefficient of variation from the 30 patients) was 31%.. Vinflunine terminal volume of distribution was large (Vdz = 1517 ± 503 L or 22.8 ± 8.3 L/kg) and terminal half-life (calculated over a 96-hour period) was 25.5 ± 3.9 h. The table below shows that vinflunine pharmacokinetics is linear in the range of administered doses (from 30 mg/m² to 400 mg/m2) in cancer patients.

Figure 1. Relationships between Vinflunine AUCinf and dose (mg/m²) after the first IV Vinflunine administration (n = 30 observations)



- Special populations

Impaired renal function

A pharmacokinetic phase I study in patients with renal impairment is ongoing. An interim analysis on 13 patients with moderate impairment (40 ml/min ≤ CrCl ≤ 60 ml/min) and on 9 patients with severe impairment (20 ml/min ≤ CrCl < 40 ml/min) indicated a decreased elimination of both vinflunine and DVFL when CrCl is decreased. This is further confirmed by the population pharmacokinetic analysis (56 patients with CrCl between 20 ml/min and 60 ml/min), showing that vinflunine clearance is influenced by the creatinine clearance value (Cockcroft and Gault formula). Dose adjustments are recommended in patients with moderate and severe renal impairment(see section 4.2 of the SPC).

Two doses are proposed in the SPC: Moderate renal impairment 280 mg/m² (a 12.5% dose decrease), Severe renal impairment 250 mg/m² (a 22% dose decrease)

Impaired hepatic function
A phase I PK dose adjusted study of IV vinflunine in cancer patients with liver dysfunction was carried out to determine the recommended dose of vinflunine and to investigate the PK and tolerability of IV vinflunine in cancer patients with chronic liver dysfunction. Three groups were scheduled according to the liver dysfunction and the patients received 320 mg/m² (groups 1 and 2), 250 mg/m² (groups 2 and 3) or 200 mg/m² (group 3) on day 1 every 3 weeks depending on tolerance.

No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients presenting varying degrees of hepatic impairment, compared to patients with normal hepatic function. This is further confirmed by the population pharmacokinetic analysis (absence of relationship between vinflunine clearance and biology markers of hepatic impairment). However, dose adjustments are recommended in patients with level 2 or 3 liver impairment (see section 4.2 of the SPC).

According to pharmacokinetic analysis and safety data the recommended doses in this specific population are as follows:

- In patients with mild liver dysfunction the recommended dose of vinflunine is 320 mg/m² given on day 1 every 3 weeks.
- For patients with moderate chronic liver dysfunction the recommended dose of vinflunine is 250 mg/m² once every 3 weeks
- In patients with severe chronic liver dysfunction the recommended dose of VFL is 200 mg/m² once every 3 weeks.

Gender, race, weight, elderly, children
No specific studies were submitted with regards to gender, race or weight. No specific studies in children were submitted either. According to the population pharmacokinetic analysis, neither gender nor Performance Status (ECOG score) had an impact on vinflunine clearance which is directly proportional to body surface area.A study in elderly patients is ongoing.

- Pharmacokinetic interaction studies

In vitro
Studies using human biomaterials (microsomes, hepatocytes) or human biological samples (e.g.: blood, plasma, urine and faeces) were performed to determine the binding characteristics of vinflunine, its metabolism and potential in vitro drug-drug interaction. CYP 3A4 is the major cytochrome enzyme involved in vinflunine metabolism and therefore strong inhibitors of CYP 3A4 are likely to affect the metabolism of vinflunine. An in vitro drug-drug interaction (DDI) study was carried out with selected drugs.

A pharmacokinetic interaction between vinflunine and pegylated/liposomal doxorubicin was observed, resulting in a 15% to 30% apparent increase in vinflunine exposure and a 2 to 3-fold apparent decrease of doxorubicin AUC, whereas doxorubicinol metabolite concentrations were not affected. According

to an *in vitro* study, such changes could be related to an adsorption of vinflunine on the liposomes and a modified blood distribution of both compounds. Therefore, caution should be excercised when this type of combination is used.

Twenty-five drugs were screened to assess the risk of DDI on vinflunine metabolism (Anastrozole, Cyclophosphamide, Docetaxel, Doxorubicin, Epirubicin, Imatinib, Gefitinib, Paclitaxel, Aminoglutethimide, Fluconazole, Fluoxetine, Itraconazole, Morphine, Norfluoxetine, Omeprazole, Ondansetron, Acenocoumarol, Ketoconazole, Methadone, Metoclopramide, Midazolam, Nifedipine, Phenprocoumon, Ritonavir, Testosterone). The risk of drug-drug interaction was evaluated on Weaver's algorithm. The results showed that: Ketoconazole, Itraconazole and Ritonavir may inhibit vinflunine metabolism, DDI may be suspected for paclitaxel and docetaxel, and DDI was unlikely for the other 20 drugs.

Thus, A possible interaction with paclitaxel and docetaxel (CYP3 substrates) has been suggested from an *in vitro* study (slight inhibition of vinflunine metabolism). No specific clinical studies of vinflunine in combination with these compounds have been carried out yet.

In vivo

A phase I study evaluating the effect of ketoconazole treatment (a potent CYP3A4 inhibitor) on vinflunine pharmacokinetics indicated that co-administration of ketoconazole (400 mg orally once daily for 8 days) resulted in a 30% and 50% increase of blood exposures to vinflunine and its metabolite 4Odeacetyl-vinflunine (DVFL), respectively.

Therefore the concomitant use of vinflunine and potent CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole and grapefruit juice) or inducers (such as rifampicine and *Hypericum perforatum* (St John's wort)) should be avoided since they may increase or decrease vinflunine and DVFL concentrations (see section 4.4 and 5.2 of the SPC). Based on these data and safety results, the recommended dose of vinflunine is defined as 160 mg/m² when co-administered with 400 mg of ketoconazole.

Risk of DDI was assessed in vinflunine combined chemotherapy with cisplatin (CDDP), with carboplatin (CBDCA), with liposomal doxorubicin, with doxorubicin, with capecitabine, and with gemcitabine. The last 3 studies are still ongoing while the first 3 are completed. A pharmacokinetic interaction between vinflunine and pegylated/liposomal doxorubicin was observed, resulting in a 15% to 30% apparent increase in vinflunine exposure and a 2 to 3-fold apparent decrease of doxorubicin AUC, whereas doxorubicinol metabolite concentrations were not affected. According to an *in vitro* study, such changes could be related to an adsorption of vinflunine on the liposomes and a modified blood distribution of both compounds. Therefore, caution should be excercised when this type of combination is used..

Overall, no pharmacokinetic interaction was observed in patients when vinflunine was combined with either cisplatin, carboplatin, capecitabine, doxorubicin or gemcitabine.

- Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been submitted.

Pharmacodynamics

No healthy subject pharmacodynamic study reports were submitted. The pharmacodynamic properties of vinflunine have been studied in cancer patient populations.

- Mechanism of action

No studies were submitted.

- Primary and Secondary pharmacology

Primary pharmacology

Three phase I trials were conducted (VFL 981, VFL 991 and VFL 992) with the main objective of determining the Maximum Tolerated Dose (MTD) and the Recommended Dose (RD). MTD and the RD were determined for each schedule of vinflunine administration: once every 3 weeks (on day1), weekly administration (on day 1), and twice every 3 weeks (on days 1 and 8).

Table 17. Vinflunine - Phase I studies

Trial/Schedule	**VFL 981** **D1 Q 3 Weeks** (CSR L00070 IN 98 101) See 2.7.6, see file	**VFL 991** **Weekly** (CSR L00070 IN 99 101) See 2.7.6, see file		**VFL 992** **D1D8 Q 3 Weeks** (CSR L00070 IN 99 102) See 2.7.6, see file
		Pretreated	**Non-pretreated**	
N° of Patients	31	14	26	16
Dose Range mg/m²	30-400	120-190	150-250	170-210
MTD/RD	MTD= 400 mg/m² RD= 350 mg/m²	MTD= 150 mg/m² RD= 120 mg/m²	MTD= 250 mg/m² RD= 150 mg/m²	MTD= 190 mg/m² RD= 170 mg/m²
Response	Renal: 1PR Breast: 2PR	-	-	-

VFL 981

This was a phase I study, assessing the pharmacokinetics of vinflunine given as a 10 minute infusion once every 3 weeks. The study was a dose escalating phase I multi-centre (3 centres in France), open label, non-randomised trial. The study was carried out between 1st December 1998 and 23rd March 2000. The primary objective was to determine the MTD of vinflunine in cancer patients (several tumour types). Secondary objectives were to determine the qualitative and quantitative toxicities of vinflunine, their duration and reversibility, to determine the pharmacokinetics of vinflunine, to search for relationships between the pharmacokinetics of vinflunine and clinical toxicities and to assess anti-tumour activity in patients with measurable and or evaluable disease. Vinflunine was given intravenously as a 10 minute infusion at a fixed dose and repeated every 21 days according to the observed toxicities.

31 patients were evaluable. The MTD of vinflunine administered in a 10 minute infusion every 3 weeks is 400 mg/m². The RD for further trials is 350 mg/m² every 3 weeks. This dose was evaluated in 6 patients for a total of 11 cycles, having an acceptable safety profile. Three responses were seen: 2 at 400 mg/m² and 1 at 350 mg/m². The pharmacokinetics of vinflunine was shown to be linear with the administered doses. Inter-individual variability was moderate. Leucopenia and neutropenia were correlated to vinflunine exposure.

VFL 991

This was a phase I study, assessing the pharmacokinetics of vinflunine given as a 10-minute infusion on a weekly schedule. The study was a dose escalating phase I multi-centre (3 centres - France, Switzerland, Belgium), open label, non-randomised trial. The study was carried out between the 4th October 1999 and the 18th June 2003. The primary objective was to determine the MTD of vinflunine in cancer patients (several tumour types). Following amendment 3 (April 12th, 2000) it was decided to determine separately MTD of weekly vinflunine when administered to either pre-treated patients (Group A) or previously untreated patients (chemonaive patients, Group B). Secondary objectives included determination of the qualitative and quantitative toxicities of vinflunine, to define their duration and reversibility, to determine the pharmacokinetics of vinflunine, to explore the reproducibility over administrations after repeated administration, to document intra and inter-

individual variability and to search for relationship between the pharmacokinetics of vinflunine to clinical toxicities observed and to assess anti-tumour activity.

In Group A, 14 patients were evaluated in 3 dose levels of weekly vinflunine. The MTD was reached at 190 mg/m²/week and the RD established at 120 mg/m²/week. In Group B, 26 chemonaive patients, the MTD was not determined even if high doses (250 mg/m²) were investigated; the RD was established at 150 mg/m²/weekly. In both groups, dose limiting toxicities consisted of haematological related toxicities, infection, severe neutropenia and febrile neutropenia. A single patient in group A presented with a transient increase in liver enzymes (declared as a DLT). No other significant modification in liver enzymes was seen. The recommended doses were associated with a good tolerance profile, mainly consisting of mild nausea and vomiting, no severe neutropenia, no thrombocytopenia or anaemia. Leucopenia and neutropenia were correlated to vinflunine exposure.

VFL 992
This was a phase I study, assessing the pharmacokinetics of vinflunine given as a 10-minute infusion on days 1 and 8 every 3 weeks a weekly schedule. The study was a dose escalating phase I multi-centre (France, UK), open label, non-randomised trial. The study was carried out between 21st October 1999 and 1st September 2000. The primary objective was to determine the MTD of vinflunine in cancer patients (several tumour types). Secondary objectives included determining the qualitative and quantitative toxicities of vinflunine given, to define their duration and reversibility, to explore the pharmacokinetics reproducibility over cycles of vinflunine after repeated administrations, to document intra and inter-individual variability at different dose levels, to search for relationship between the pharmacokinetics of vinflunine and the observed clinical toxicities and to assess anti-tumour activity.

The MTD of vinflunine administered in a 10-minute infusion on days 1 and 8 every 3 weeks is 190 mg/m². RD for further trials is 170 mg/m². This dose was evaluated in 6 patients for a total of 10 cycles with an acceptable safety profile. Leucopenia and neutropenia were correlated to vinflunine blood exposure.

Secondary pharmacology
No secondary pharmacology studies were submitted.

- Pharmacodynamic interactions with other medicinal products or substances

Drug-drug interaction studies are ongoing.

- Genetic differences in PD response

No data was submitted concerning genetic determinants of drug response.

Discussion on clinical pharmacology aspects

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. The approach to determine the optimally tolerated dose of vinflunine was satisfactory and allowed for the exploration of several different posologies in numerous patients. Based on the analysis of the safety, pharmacokinetics and clinical activity from the 3 dose schedules evaluated at Phase I, vinflunine treatment once every 3 weeks was considered optimal. The recommended dose was established at 350 mg/m² every 3 weeks. This dose was carried forward for further phase II evaluation.

Posology

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

In case of WHO/ECOG Performance Status (PS) of 1 or of 0 and prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m². In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

Dose adjustment due to toxicity

Table 1: Dose adjustments due to toxicity

Toxicity	**Dose adjustment**				
	Vinflunine initial dose of 320 mg/m²			**Vinflunine initial dose of 280 mg/m²**	
(NCI CTC v 2.0)*	First Event	2nd consecutive event	3rd consecutive event	First Event	2nd consecutive event
Neutropenia Grade 4 (ANC< 500/mm^3)> 7 days	280 mg/m²	250 mg/m²	Definitive Treatment discontinuation	250 mg/m²	Definitive Treatment discontinuation
Febrile Neutropenia (ANC< 1,000/mm^3 and fever ≥ 38,5 °C)					
Mucositis or Constipation Grade 2 ≥ 5 days or ≥ 3 any duration					
Any other toxicity Grade ≥ 3 (except Grade 3 vomiting or nausea)					

*National Cancer Institute, Common Toxicity criteria (NCI-CTC)

In patient with ANC < 1,000/mm^3 or platelets < 100,000/mm^3 at the day of administration, the treatment should be delayed until recovery (ANC≥ 1,000/mm^3 and platelets ≥ 100,000/mm^3). If recovery has not occurred within 2 weeks, the treatment will be definitively discontinued.
In case of Grade 4 neutropenia (ANC < 500/mm^3) for more than 7 days or febrile neutropenia, dose adjustment is recommended (see table above).
The day of infusion, in case of Grade ≥ 2 organ toxicity, the treatment should be delayed until recovery to Grades 0, 1 or initial baseline status.

Special populations

Hepatic impairment

Vinflunine pharmacokinetics is not modified in patients with three levels of impaired liver function (see table below and section 5.2), however based on hepatic biologic parameter modifications following vinflunine administration (gamma glutamyl transferases (GGT), transaminases, bilirubin), the dose recommendations are as follows:

Table 2: Dose adjustments due to hepatic impairment

Level and posology	Child Pugh Grade		Prothrombine time		Bilirubin		Transaminases		Gamma Glutamyl Transferases
Level 1 320 mg/m²	-	-	> 70% NV	and	> ULN and	and/ or	> 1.5xULN and	and/ or	> ULN and

					≤ 1.5xULN		≤ 2.5xULN		≤ 5xULN
Level 2 250 mg/m²	A	Or	≥ 60% NV	and	> 1.5xULN and ≤ 3xULN	and	> ULN	and/ or	> 5xULN
Level 3 200 mg/m²	B	or	≥ 50% NV	and	> 3xULN	and	> ULN	and	> ULN

NV: Normal Value ULN: Upper Limit of Normal

Vinflunine was evaluated neither in patients with Child-Pugh grade C, nor in patients with prothrombin time<50%NV or with bilirubin >5xULN or with transaminases >6xULN or with Gamma Glutamyl Transferases (GGT)>15xULN.

Renal impairment

In the clinical studies, patients with CrCl (creatinine clearance)> 60 ml/min were included and treated at the recommended dose.

In patients with moderate renal impairment (40 ml/min ≤ CrCl ≤ 60 ml/min), the recommended dose is 280 mg/m² given once every 3 weeks.

In patients with severe renal impairment (20 ml/min ≤ CrCl < 40 ml/min) the recommended dose is 250 mg/m² every 3 weeks. (see section 5.2).

Elderly (> 65 years)

In the clinical studies, 103 patients ≥ 75 years old and 374 patients ≥ 65 and < 75 years old were treated at the recommended dose of vinflunine. No significant differences in safety were observed in these two age groups. No specific dose recommendation is necessary in the elderly.

Paediatric use

Use in children – there is no relevant indication for use of Javlor in children

Method of administration

Javlor must be diluted prior to administration. Javlor is for single use only.

For instructions on dilution before administration, see section 6.6 of the SPC

Javlor MUST ONLY be administered intravenously. Intrathecal administration of Javlor may be fatal. Javlor must be administered by a 20minute intravenous infusion and NOT be given by rapid intravenous bolus.

Either peripheral lines or a central catheter can be used for vinflunine administration. When infused through a peripheral vein, vinflunine can induce venous irritation (see section 4.4). In case of small or sclerosed veins, lymphoedema, recent venipuncture at the same vein, the use of a central catheter may be preferred. To avoid extravasations it is important to be sure that the needle is correctly introduced before starting the infusion.

In order to flush the vein, administration of Javlor concentrate for solution for infusion should always be followed by at least an equal volume of sodium chloride 9 mg/ml (0.9%) solution for infusion or of glucose 50 mg/ml (5%) solution for infusion.

For detailed instructions on administration, see section 6.6 of the SPC.

Recommended comedication

In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration (see section 4.4 of the SPC).

In addition, the following concerns were identified with regards to the clinical pharmacology data submitted as part of this dossier.

1. The CHMP requested that inter-individual differences in the activity and expression of the metabolising enzymes should be discussed (CYP3A4 polymorphism). Given that all metabolites of VFL formed through CYP3A4 are inactive, any modification of CYP3A4 activity from a genetic mutation would impact VFL by either decreasing efficacy (lower VFL blood exposure) or increasing toxicity (higher VFL blood exposure). According to the reflection paper (CHMP/EMEA/1285717/2006), the most important polymorphic cytochrome P450 enzymes are CYP2D6, CYP2C9 and CYP2C19. This is in accordance with the figure provided by the applicant which shows that the estimated known-genetic fraction to CYP3A4 variability in vivo is lower than the other polymorphic CYPs. No specific in vivo study was carried out to investigate the genetic polymorphism impact of CYP3A4 on the PK of VFL, however, no putative relationships between CYP3A4 polymorphism and the PK of vinca alkaloids is reported in the literature, suggesting that none of the known allelic variants of CYP3A4 accounted for variability in CYP3A4 activity.

2. The CHMP requested that the role of biliary excretion be further discussed. The results from the PK and safety study in patients with mild to severe liver dysfunction supported the Applicant's position that a decrease in biliary excretion should have relatively little impact on VFL and DVFL PK (the active moieties).

3. The applicant was requested to commit to providing the results of the ongoing drug-drug interaction (DDI) studies, as follow-up measures. Further discussion on the implications of the suspected DDI for paclitaxel and docetaxel were also requested by the CHMP, including additional wording to the product literature. According to Weaver's algorithm and the FDA Guidance, the potential DDI risk when combined with VFL was likely for ketoconazole, itraconazole and Ritonavir, which may significantly inhibit VFL metabolism in the clinical setting. An in vitro study also suggested a possible DDI for paclitaxel and docetaxel. Therefore, although vinflunine is not intended for combination with either docetaxel or paclitaxel, the applicant amended section 4.5 of the SPC with additional wording: ' A possible interaction with paclitaxel and docetaxel (CYP3 substrates) has been suggested from an *in vitro* study (slight inhibition of vinflunine metabolism). No specific clinical studies of vinflunine in combination with these compounds have been carried out yet'.

4. The applicant was requested to provide further information on the linearity of VFL pharmacokinetics (Study L0070 98 IN 101 Q0) over range of VFL dose from 30 mg/m2 up to 400 mg/m2, by for example providing a table and its graphic representation of AUClast versus Cmax for different doses and adjusted to the dose 320 mg/m2. From the applicant's responses, the PK linearity of VFL was investigated through different approaches and PK parameters calculations. Dose-adjusted PK parameters were consistent across strata of doses and they are supported by graphical displays. Furthermore, the analyses based on the empirical Bayes confirmed the results of the first evaluation of pooled data from early phase I studies and based on non-compartmental AUC calculations. The SPC was amended accordingly.

5. The applicant was requested to provide updated results for both studies L00070 IN 113 (patients with renal impairment) and L00070 IN 114 (elderly patients) as follow-up measures.

6. The applicant was asked to comment on any plan for a paediatric development. The CHMP agreed that TCCU is predominantly present in adults, in fact, the incidence of bladder cancer increases with age; and that carcinoma of the bladder is extremely rare in children so that it was included in the list of class condition waivers for paediatric requirements by the PDCO. However, bladder cancer in adolescents may develop as a consequence of alkylating-agent chemotherapy given for other childhood tumours or leukaemia. In its responses, the applicant will request a waiver to the EMEA for the TCCU indication, which will be evaluated by the Paediatric Committee. However, the CHMP considered that the potential off-label use in children still justified a paediatric development for relevant conditions, where there is a paediatric need. As a result of this discussion, the lack of data in children and adolescent was reflected in section 4.2 of SPC as follow: 'Use in children – there is no relevant indication for use of Javlor in children'.

7. The applicant was requested to submit the final results of study BMS CA183009 (effect of ketoconazole on the VFL PK). The CHMP considered that the final results were in accordance with

the preliminary results of the interim analysis performed on 10 patients. Though no precise dose adjustments are propose in the SPC, adequate warnings were included to discourage the concomitant use of strong CYP3A4 inhibitors in section 4.5 of SPC.

8. VFL is apparently a P-glycoprotein substrate as it displays the classic MDR profile. Therefore the CHMP requested that the applicant discuss the risk for clinically significant interactions with P-glycoprotein inhibitors/inducers, and to address whether information on P-glycoprotein should be added to section 4.5 of the SPC.

The Applicant provided preclinical data to suggest that vinflunine, as with other vinca alkaloids, is a Pgp substrate. VFL has lower affinity than either Vincristine or Vinorelbine and inter-patient variability between an oral preparation and IV formulation was minimal, suggesting that clinically significant interactions are unlikely. However, no specific PK study on vinflunine and P-glycoprotein (Pgp) were conducted to rule out a clinically meaningful interaction. To reflect this unlikely interaction, the following statement was included in section 4.5 of the SPC.

"In vitro studies showed that vinflunine is a Pgp substrate as the other vinca alkaloids, but with a lower affinity. Therefore, risks of clinically significant interactions should be unlikely."

9. In section 4.2 it has been clarified that there is no data in Child Pugh C patients. However, in section 4.4 and 5.2, still the term "severe hepatic impairment" refers to Child Pugh B patients, as this was the definition used in the Sponsor's specific study. However, the CHMP considered that this might be misleading, as in SPCs it is more common to use the term "severe hepatic impairment" for Child Pugh C patients, while Child Pugh B is denoted "moderate hepatic impairment". Therefore, to clarify the information included in the SPC relative to the dosage in the hepatic impaired patients, the following amendments were made.

Section 4.4:
"Hepatic impairment
The recommended dose should be reduced in patients with level 2 or 3 of hepatic impairment (see section 4.2)."

Section 5.2
"Pharmacokinetic in special populations
Hepatic impairment
No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients presenting varying degrees of hepatic impairment, compared to patients with normal hepatic function. This is further confirmed by the population pharmacokinetic analysis (absence of relationship between vinflunine clearance and biology markers of hepatic impairment) However, dose adjustments are recommended in patients with level 2 or 3 liver impairment (see section 4.2)."

Section 4.2:
"Special populations
Hepatic impairment
Vinflunine pharmacokinetics is not modified in patients with three levels of impaired liver function (see table below and section 5.2), but mainly based on hepatic biologic parameter modifications (gamma glutamyl transferases (GGT), transaminases, bilirubin), the dose recommendations are as follows:

Table 2. Dose adjustments due to hepatic impairment

Level and posology	Child Pugh Grade		Prothrombine time		Bilirubin		Transaminases		Gamma Glutamyl Transferases
Level 1 320 mg/m²	-	-	> 70% NV	and	> ULN and ≤ 1.5xULN	and/ or	> 1.5xULN and ≤ 2.5xULN	and/ or	> ULN and ≤ 5xULN
Level 2 250 mg/m²	A	or	≥ 60% NV	and	> 1.5xULN and ≤ 3xULN	and	> ULN	and/ or	> 5xULN
Level 3 200 mg/m²	B	or	≥ 50% NV	and	> 3xULN	and	> ULN	and	> ULN

NV: Normal Value ULN: Upper Limit of Normal

Vinflunine was evaluated neither in patients with Child-Pugh grade C, nor in patients with prothrombine time < 50% NV or with bilirubin > 5xULN or with transaminases > 6xULN or with Gamma Glutamyl Transferases (GGT)> 15xULN."

Clinical efficacy

The clinical development programme for vinflunine in second-line treatment in patients with TCCU after platinum-containing chemotherapy regimens included 3 phase I trials (VFL 981, 991 and 992), 2 phase II studies (VFL 202 and CA001) and 1 randomised Phase III study (VFL 302). The table below summarises the phase II/III studies.

Table 18. Summary of Phase II/III studies

Study N°	Design	Diagnosis/Setting	Nb of patients treated	Test Product (s): Dosage Regimen	Efficacy endpoints
VFL 202	Phase II open-label, single-arm study of VFL as 2nd therapy	Advanced bladder TCC after failure on a platinum-containing regimen	51	VFL at initial dose of 320 mg/m² q3w	Primary –ORR Secondary - duration of response; PFS; OS.
CA 001	Phase II, open-label, single-arm study of VFL as second-line therapy	Advanced or metastatic TCC of the urothelium after failure on a platinum-containing regimen	151	VFL at initial dose of 320 or 280 mg/m² q3w	Primary - RR Secondary - duration of response; TTR; disease control rate; PFS; OS.
VFL 302	Phase III, randomised, open-label study in 2nd line therapy with VFL + BSC vs BSC	Advanced TCC of the urothelium after failure on a platinum-containing regimen	VFL: 248; BSC: 117	VFL at initial dose of 320 or 280 mg/m² q3w + BSC vs BSC	Primary - OS Secondary - patient benefit, clinical benefit; RR; time to response; duration of response; PFS; DR

- Dose response study(ies)

Three phase I trials with vinflunine monotherapy have been conducted exploring 3 different administration schedules: (1) day 1 every 3 weeks, 2) day 1 every week, and 3) days 1&8 every 3 weeks. Based on safety, pharmacokinetics and clinical activity, the schedule of vinflunine administered on day 1 every 3 weeks was selected for further clinical development (VFL 981). Dose limiting toxicities were neutropenia, constipation and mucositis and the recommended dose for this schedule was 350 mg/m2 iv q3w. A strong correlation between vinflunine AUC and maximum neutrophil count decrease from baseline were demonstrated. Preliminary evidence of antineoplastic activity was documented (tumour responses were observed in 1 renal and 2 breast cancer patients).

Table 19. Dose Response Studies

Trial/Schedule	**VFL 981 D1 q 3 w**	**VFL 991 Weekly**		**VFL 992 D1D8 q 3 w**
		Pre-treated	**Non pre-treated**	
N° of Patients	31	14	26	16

Dose Range mg/m²	30-400	120-190	150-250	170-210
MTD/RD	MTD= 400 mg/m² RD= 350 mg/m²	MTD= 150 mg/m² RD= 120 mg/m²	MTD= 250 mg/m² RD= 150 mg/m²	MTD= 190 mg/m² RD= 170 mg/m²
Response	Renal: 1PR Breast: 2PR	-	-	-

Starting in October 2000, an international program of Phase II studies with vinflunine as a single agent was undertaken in a wide range of solid tumours. In these early studies, vinflunine was administered at a dose of 350 mg/m² every 3 weeks according to the phase I clinical trial recommendation. A preliminary safety analysis performed after the enrolment of 60 patients in different trials, however, showed an exceedingly high rate of myelotoxicity (64% of patients had Grade 3/4 events, 15% developed febrile neutropenia). Twenty-two patients (36.6%) out of the 60 patients who were exposed to 350 mg/m², experienced at least 1 study treatment related SAE, including 4 (6.7%) study treatment related deaths within the 30 days following the last vinflunine administration. These findings prompted a reduction of the recommended dose to 320 mg/m² every 3 weeks for all patients subsequently included in clinical trials. This dose recommendation was later further reduced to 280 mg/m2 in patients at higher risk of myelosuppression (PS > 1, prior pelvic radiotherapy).

- Main study(ies)

Study VFL 302: *"Prospective, randomised, phase III trial of IV vinflunine plus best supportive care as second line therapy versus best supportive care after a platinum-containing regimen, in patients with advanced transitional cell carcinoma of urothelial tract".*

METHODS

Study Participants

Subject Inclusion Criteria

- Patient's written informed consent must be obtained and documented prior to beginning specific procedures for study and follow up
- Histologically TCCU. Locally advanced or metastatic disease;
- Progressive disease, patients who had failed or progressed after first line platinum-containing chemotherapy for advanced or metastatic disease. First line chemotherapy was defined as patients receiving at least 2 cycles. In cases of clear evidence of PD after 1st cycle of previous chemotherapy, patients were accepted and stratified as refractory patients
- Previous systemic chemotherapy must have been stopped 30 days before the randomisation with full recovery from any related toxicity
- Prior radiation was allowed < 30% of the bone marrow and must have been completed 30 days before randomisation with full recovery of any related toxicity
- Measurable and/or non-measurable disease using the RECIST criteria defined as:
  Measurable disease: lesions that can be accurately measured in at least one dimension and which have not been previously irradiated: with longest diameter ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT scan or MRI.
  Non-measurable disease: lesions which have been previously irradiated: with longest diameter < 20 mm with conventional CT scan or < 10 mm with spiral CT scan or MRI and truly non measurable lesions including bone lesions, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonitis;
- Age ≥ 18 years
- ECOG WHO PS 0 or 1
- Estimated life expectancy at least 12 weeks
- Adequate haematological function:
  Absolute neutrophil count ≥ 1.5 x 10^9 /L and platelets ≥ 100 x 10^9/L

- Adequate hepatic function:
  Bilirubin ≤ 1.5 x UNL transaminases ≤ 2.5 x UNL (< 5 x UNL only in case of liver metastases);
- Adequate renal function:
  Calculated clearance of creatinine (≥ 40 ml/min) (Cockcroft and Gault formula)
- ECG without significant modifications with clinical consequences (within 7 days before randomisation)

Subject Exclusion Criteria
Patients were excluded if they had:

- Non-transitional cell carcinoma of the urothelial tract (adenocarcinoma, squamous cell carcinoma or other)
- Known brain metastases or leptomeningeal involvement. Brain CT-scans or MRI were not required to rule this out unless there was clinical suspicion of central nervous system (CNS) involvement;
- Peripheral neuropathy grade ≥ 2 by NCI CTC version 2.0;
- History of serious or concurrent illness or uncontrolled medical disorder; any medical condition that might be aggravated by treatment or which could not be controlled:
- Active infection requiring antibiotics within 2 weeks before the beginning of the study randomisation
- Uncontrolled cardiac arrhythmia
- Unstable diabetes mellitus,
- Uncontrolled hypercalcaemia > 2.9 mmol/L (or > grade 1 NCI CTC version 2.0)
- Patients with concurrent heart failure NYHA (class III-IV) or patients with unstable angina pectoris, patients with myocardial infarction within 6 months and/or poorly controlled hypertension were excluded.
- Patients who received more than one previous systemic chemotherapy for advanced or metastatic disease
- Patients who received neoadjuvant or adjuvant chemotherapy;
- Patients who received any other investigational or anti-cancer therapy 30 days before the randomisation
- Other malignancies except adequately treated basal carcinoma of the skin or *in-situ* cervix carcinoma or incidental prostate cancer (T1a, Gleason score 6, PSA < 0.5 ng/ml) or any other tumour with a free interval > 5 years
- Pregnant or lactating women
- Men or women of childbearing potential not employing adequate contraception
- Psychological, familial, sociological or geographical conditions which do not permit protocol compliance and medical follow-up

Subjects had histologically proven TCCU. All patients had received first-line platinum-containing chemotherapy, mainly for metastatic disease, except 3 patients in the vinflunine + BSC group and 6 patients in the BSC group who received adjuvant or neoadjuvant prior treatment. Gemcitabine/platinum containing regimens were the most common (75% in the VFL+BSC group, 70% in the BSC group). Of the platinum agents, cisplatin was the most commonly used, given in 65% of the vinflunine + BSC group and 73% of the BSC group, then carboplatin, given in 30% of the vinflunine + BSC group and 20% of the BSC group.

Patients were withdrawn from the study for the following reasons:

VFL+BSC Group
• disease progression at any time,
• symptomatic deterioration – patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression,
• patient refusal of further treatment,
• adverse events (AEs)/toxicity,

• patient non-compliance,
• investigator non-compliance,
• other reason (to be documented).

BSC Group
• inability to meet every 3-week schedule, patients were followed every 3 weeks until the end of the 18-week period (or death),
• patients who received any concomitant systemic chemotherapy were to be followed every 3 weeks until the end of the 18-week period (or death),
• patient refusal to continue to participate in the study,
• patient non-compliance,
• investigator non-compliance,
• other reason (to be documented)

Centres from the following countries participated in the trial: Argentina, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Russia, Serbia Montenegro, Slovakia, Spain, South Africa, Switzerland, United Kingdom

Treatments

The study had two treatment arms: vinflunine (VFL) and Best Standard of Care (BSC) or BSC alone. In the vinflunine + BSC group, treatment was administered until documented progression. All lesions were regularly assessed every 42 days. In the BSC group, visits were recorded until completion of the 18-week.

Arm A – vinflunine + BSC
VFL was administered every 21 days as a 20-minute infusion. Each 21-day period was defined as a cycle of treatment. There were 2 different starting doses of VFL used in this study tailored according to the patient: 320 mg/m² and 280 mg/m².Treatment was discontinued following progressive disease, unacceptable toxicity, intercurrent illness or other reactions which would require discontinuation of the drug and request by the patient to withdraw. The follow-up period was the time from 30 days after the last study treatment administration.

Arm B – BSC
BSC was given according to institutional standards (including palliative radiotherapy, antibiotics, analgesics, steroids, transfusion). Treatment was discontinued following completion of the 18-week period counting from the day of randomisation, receiving a systemic anticancer therapy due to documented progressive disease compared to baseline, request by the patient to withdraw and patient inability to meet the every 3-week schedule.

Patient accrual was planned to be completed within 24 months from the beginning of the study (May 21st 2003). The study duration phase was planned to continue until the last patients withdrew from the treatment (November 6th 2006) After withdrawal from the study treatment, each patient will be followed until death.

Objectives

The primary objective was to compare overall survival (defined as the interval between randomisation and death or last follow up) in patients with advanced TCCU previously treated with a platinum-containing chemotherapy as first line treatment. The main objective was to show survival superiority in the vinflunine arm compared to best supportive care (BSC) alone, based on the statistical hypothesis that the median survival time for the vinflunine + BSC arm would be 6 months compared to a median survival time for the BSC only patients of 4 months.

The secondary objectives were :
- to compare patient benefit through a quality of life questionnaire (EORTC QLQ-C30) and clinical benefit parameters.

- to compare the safety profile in both study arms
- to assess response rate, time to response, response duration and progression-free survival in patients treated with vinflunine +BSC.

Outcomes/endpoints

The primary endpoint of the study was overall survival. Secondary endpoints were progression-free survival, response rate, disease control/rate, quality of life and clinical benefit.

Sample size

A total of 330 randomised evaluable patients were enrolled. The vinflunine + BSC arm had 220 randomised evaluable patients and the BSC only arm had 110 randomised evaluable patients. To accommodate an anticipated 10% loss of patients to follow-up, 364 patients should have been included.

Randomisation

Patients were randomised 2:1 to vinflunine + BSC or BSC alone. Patient randomisation was limited to stratification by study site and whether a patient was refractory to prior chemotherapy (defined as progression within the first 2 cycles of a prior platinum-containing regimen). Randomisation was performed by the Biometric department of IRPF.

Blinding (masking)

The phase III study was an open label study.

Statistical methods

The objective of the protocol was to show a significant survival superiority in the vinflunine + BSC arm versus the BSC only arm. The sensitivity analyses for the primary efficacy parameter included:
- overall survival analysed in the per protocol population.
- overall survival censored at the time (start date) of further chemotherapy in the randomised population and in the statistical analysis plan per protocol population.

For patients who had not died, survival duration was censored at the date of last news if the patient was lost to follow-up or reached the time point of analysis without a known record of death. For patients who received secondary chemotherapy, survival duration was censored at the start date of the secondary chemotherapy.

The estimation of the number of events was based on the following clinical hypotheses:
- the median survival time for vinflunine + BSC arm is 6 months.
- the median survival time for BSC arm is 4 months.

A total of 290 events were assumed to be needed to allow the detection of a survival superiority between both arms. The primary analysis was based upon the stratified log rank test performed at 0.05 level. The primary analysis set was the intent to treat population. A Cox multivariate analysis on survival was performed in order to take into account prognostic factors (treatment group, alkaline phosphatase (< median, ≥ median), haemoglobin (< median, ≥ median), visceral metastases (yes, no), WHO PS (0, ≥1), radiotherapy of the pelvis (yes, no), and the presence of lymph nodes (yes, no)). Survival information was collected approximately every 6 weeks during the first 6 months and then every 2 months until death.

Secondary objectives were to compare patient benefit through a quality of life questionnaire (EORTC QLQ-C30) and clinical benefit parameters, to compare the safety profile in both arms and to assess response rate (according to RECIST, Independent Review Committee (IRC) reviewed tumour assessments with CR and PR), time to response, response duration and progression free survival.

Statistical methods for categorical variables: the x2 test was performed to compare proportions or replaced by Fisher exact test if the expected frequency in one cell of the contingency table was less than 5. The 95% CI for proportions was computing following the exact method.

Statistical method for ordinal variables: comparison between treatment arms was provided for ordinal data using the non-parametric Wilcoxon rank sum test.

Statistical method for continuous variables: the distribution of quantitative data was examined by the Kolmogorov-Smirnov test in order to test for normality. In case of Gaussian distribution, the comparison between treatment arms was made with a Student t-test. In case of non-Gaussian distribution, a non-parametric Wilcoxon test was performed.

Statistical methods for time to event data: Kaplan-Meier curves and life tables by treatment arm were used to describe time dependent paramenters. Confidence intervals on the median were calculated using the reflection method. Stratified Logrank tests were performed to compare the two arms for overall survival. Multivariate analyses were performed to take into account the prognostic factors. A stratified Cox proportional hazard model was applied to the data.

Statistical methods for Quality of Life data: data was analysed with a mixed effect model with change from baseline as the response. The most suitable covariance structure was chosen according to Akaike's Information Criterion and Schwartz Bayesian Criterion between unstructured, compound symmetric and autoregressive of order 1.

Populations analysed

1. Intent to treat population: all randomised patients whether treated or not were analysed in the group they were assigned by randomization.

2. Per protocol population: patients that were eligible and treated in the arm assigned by randomization.

   Eligible patients were defined as those who had no major protocol deviations from inclusion and exclusion criteria. These included the following: 1) no locally advanced or metastatic histologically proven TCC at study entry, 2) no progression after 1st line platinum-containing chemotherapy for advanced disease, 3) having received a neoadjuvant or adjuvant chemotherapy, 4) more than 1 line of chemotherapy, and 5) did not have a prohibited chemotherapy on study.

3. Evaluable for response: patients that were eligible, evaluable and treated in the arm assigned by randomization.

   To be evaluable for response patients must had received a minimum of two cycles/42 days of treatment as required by the protocol unless progression was documented before (in that case patient was considered evaluable with an early progression) and must have all baseline lesions assessed at least once after the second cycle with the same method of measurement as baseline.

4. Evaluable for safety: included all treated patients, in the treatment arm they actually received.

5. Evaluable for quality of life: included patients who completed (more than two thirds of the questions) one questionnaire within 14 days prior to randomisation and at least one questionnaire during study period at least 21 days after the beginning of study treatment or first visit for patients in BSC group. Patients were analysed in the group they were assigned by randomisation.

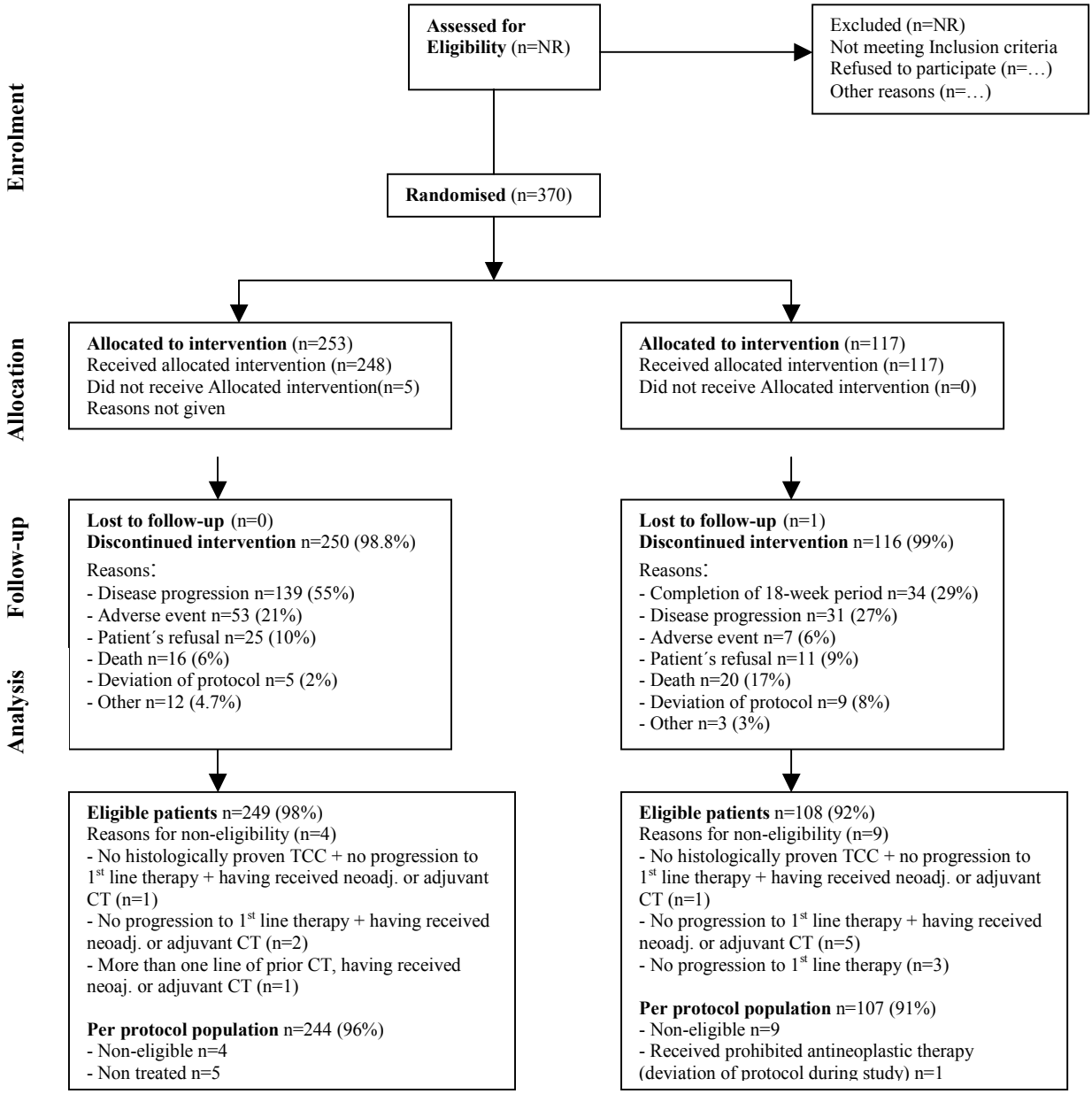
Efficacy Analysis

Primary and secondary efficacy analyses for overall survival were performed on the whole randomised population and on the pre-planned per protocol populations. Primary and secondary efficacy analyses for the other efficacy endpoints were performed on the whole randomised population and on the response evaluable population.

Additional efficacy analysis were performed based on blinded assessment by an Independent Review Panel (IRP) of patients with partial or complete responses or long stabilizations (lasting at least 4 cycles). Also, an Independent Review Committee (IRC) evaluated study-related images and a subset of selected, prospectively defined clinical information for all patients who were randomized.

Results

Participant flow



Recruitment

The date of first enrolment was 21st May 2003. The study data cut off was 30th November 2006 with a final data update on the 31st of May, 2007.

Conduct of the study

A total of 8 protocol amendments were carried out. Of importance, on May 21st 2003, all patients randomised to vinflunine + BSC were treated at 320 mg/m² every 21 days as a 20-minute infusion. On November 19th 2003, an amendment (amendment 1) was drawn up after a safety assessment was carried out on the first 10 treated patients. This amendment led to a tailored vinflunine administration as follows:

- Patients with Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) Performance Status (PS) 0 and without any previous irradiation of the pelvic area should receive VFL 320 mg/m² plus BSC
- Patients with PS 1 and patients with PS 0 with previous irradiation of the pelvic area should receive VFL as follows:
  - At 1st cycle: VFL 280 mg/m² plus BSC
  - At 2nd cycle: patients without haematological toxicities causing treatment delay should start VFL at 320 mg/m² plus BSC.
- Patients with haematological toxicities causing a treatment delay should receive VFL at 280 mg/m² plus BSC. These patients were not allowed to further dose escalate.

Thirty one protocol deviations were established, among these items 4 were considered as significant protocol deviations. A total of 116 (31%) patients had 1 or more protocol deviations: 73 (29%) in the VFL+BSC group and 43 (37%) in the BSC group. The 116 patients collectively had 26 of the 31 major protocol deviations that were pre-specified. Nine percent of bone scintigraphy and X-rays were not performed within 42 days before randomisation. The performance of bone scanning was the most common major protocol deviation (9% in both groups).

Baseline data

Baseline patient data is summarized in the table below.

Table 20. Main Baseline Characteristics- All Randomised Patients

Main Baseline Characteristics: All Randomised Patients

	VFL+BSC (N=253)	BSC (N=117)
Age (years)		
Mean (s.d)	63.5 (9.7)	63.8 (9.7)
Median (min, max)	64.2 (37, 86)	64.2 (35, 85)
Gender (n, %)		
Men	197 (77.9)	95 (81.2)
Women	56 (22.1)	22 (18.8)
WHO performance status at randomisation (n, %)		
0	72 (28.5)	45 (38.5)
1	181 (71.5)	72 (61.5)
Received a prior platinum-containing chemotherapy (n, %)	253 (100.0)	117 (100.0)
For metastatic disease	250 (98.8)	111 (94.9)
For neoadjuvant/adjuvant	3 (1.2)	6 (5.1)
Prior Therapy		
Surgery	227 (89.7)	103 (88.0)
Radiotherapy	74 (29.2)	28 (23.9)
Radiotherapy of the pelvic area at randomisation or baseline	57 (22.5)	26 (22.2)
Primary tumour type (n, %)		
Transitional cell carcinoma	253 (100.0)	117 (100.0)
Primary tumour site (n, %)		
Upper urinary tract (calyces, renal pelvis, ureters)	52 (20.6)	17 (14.5)
Bladder	201 (79.4)	99 (84.6)
Urethra	0	1 (0.9)
Stage at diagnosis		
0A +0IS	15 (5.9)	4 (3.5)
I	31 (12.3)	19 (16.2)
II	25 (9.9)	20 (17.1)
III	25 (9.9)	12 (10.3)
IV	120 (47.4)	53 (45.3)
Unknown	37 (14.6)	9 (7.7)
Treatment free interval (months): from end of prior chemotherapy to 1st dose of VFL for VFL+BSC or randomisation for BSC	**N = 245[a]**	**N = 111[a]**
Mean (s.d)	6.0 (8.0)	5.2 (5.2)
Median (min, max)	3.6 (0.9, 60.5)	3.4 (0.5, 34.6)
< 3	108 (44.1)	43 (38.7)
3 - ≤ 6	64 (26.1)	36 (32.4)
6 - ≤ 12	44 (18.0)	22 (19.8)
> 12	29 (11.8)	10 (9.0)
Refractory status at randomisation	**N = 253**	**N = 117**
Yes	33 (13.0)	15 (12.8)
No	220 (87.0)	102 (87.2)
Number of organs involved as per investigator		
1	62 (24.5)	31 (26.5)
2	87 (34.4)	39 (33.3)
≥ 3	104 (41.1)	47 (40.2)
Visceral involvement[b]	187 (73.9)	87 (74.4)

a: Only patients with first line treatment for advanced disease are considered
b: visceral involvement is defined as at least one lesion in bladder, lung, liver, stomach, colon, small bowel, pancreas, supra renal gland or kidney

Numbers analysed

ITT
Efficacy analyses for overall survival were performed on the whole randomised population (n=370, 100%), on the eligible population (n=357, 96.5%) and on the pre-planned per protocol population (n=351). Other efficacy analysis were performed on the whole randomised population (n=370, 100%) and on the response evaluable population (n=270, 72.9%).

The table below summarizes the number of participants in each group included in the analysis.

Table 21. Study VFL 302. Participants by category

	VFL 302	
	VFL + BSC	BSC
Registered[a]	253 (100.0)	117 (100.0)
Treated	248 (98.0)	117 (100.0)
Eligible	249 (98.4)	108 (92.3)
Per protocol population	244 (96.4)	107 (91.5)
Evaluable for response per investigator assessment	215 (85.0)	93 (79.5)
Evaluable for response after IRP/IRRC/IRC	185 (73.1)	85 (72.6)

Eligible patients

The eligible patient population corresponds to the whole randomised population minus ineligible patients, those with clinically significant protocol violations at baseline (i.e. violating the inclusion criteria). The eligible patient population represents the actual TCCU population targeted by the protocol (all randomised patients excluding non eligible patients: VFL+BSC: 4 patients, BSC: 9 patients: not pre-specified in the protocol).

Non-Eligible patients

Patients with significant eligibility deviation	VFL+BSC	BSC
More than 1 line of chemotherapy	1	0
No locally advanced or metastatic histologically proven TCC at study entry	1	1
No progression after 1st line platinum-containing chemotherapy for advanced disease	3	9
Patients having received a neoadjuvant or adjuvant chemotherapy	4	6
Total number of patients with clinically significant protocol deviations	**4**	**9**

Per protocol

Per protocol population corresponds to the randomised population minus non eligible patients. Per protocol population excludes 13 patients who had 1 or more significant deviations at baseline, deviations during the study and non-treated patients. Per protocol population (according to the statistical analysis plan was 244 subjects in the vinflunine + BSC arm and 107 subjects in the BSC. This population corresponds to all those randomised patients except:

- Deviations to the protocol at baseline (13 patients)
- Deviations to the protocol during study (1 patient)
- The non-treated patients (5 patients)

Outcomes and estimation

Primary Endpoint

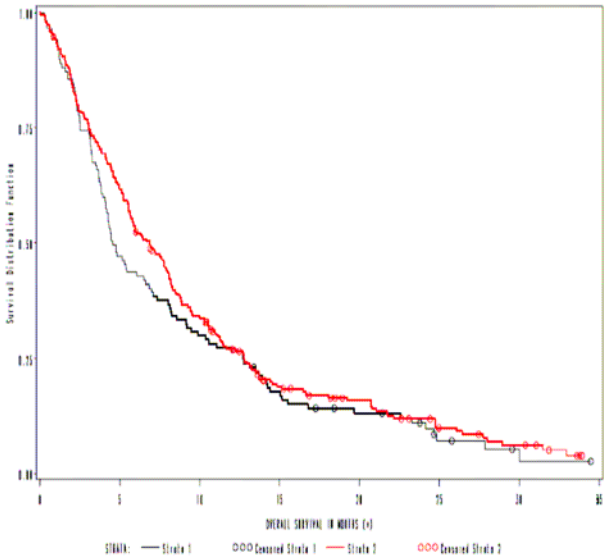
Overall Survival (OS) All randomised patients

81% patients died in the vinflunine and BSC and 88% patients died in the BSC only arm. Median OS for all randomised patients was 6.9 months in the vinflunine arm and 4.6 months in the BSC arm. The risk of death is reduced by 12% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.88 (95% CI: 0.69 - 1.12), but the OS difference between the 2 arms is not statistically significant (p=0.2868).

Overall survival data was updated 6 months after the first analysis in November, 2006. OS in the all randomised population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus

4.6 months), with a reduction of risk of death by 12%, HR 0.88 (95% CI: 0.69, 1.10). This difference is not statistically significant (p = 0.2546).

Figure 2. Overall Survival: All Randomised Patients



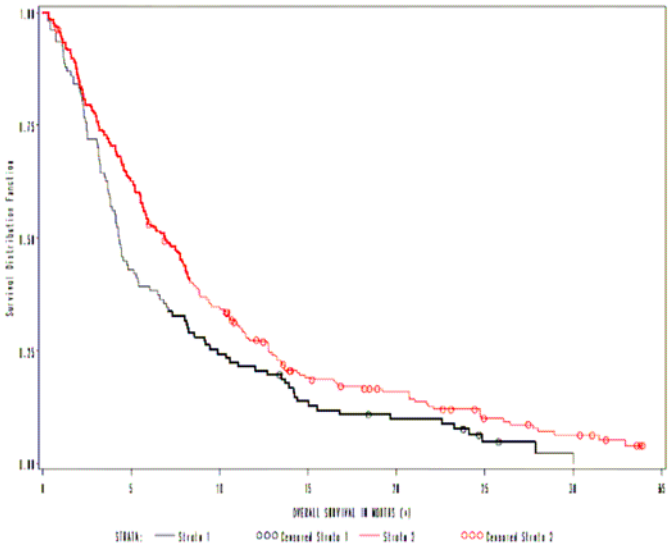
	VFL+BSC (N=253)	BSC (N=117)
No. of events	223	108
No of censored (%)	30 (11.9)	9 (7.7)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.6 (4.1,6.6)
Hazard ratio (95% CI)	0.88 (0.69, 1.10)	
p value[a]	0.2546	

CSR VFL 302 Additional efficacy analysis, Table 11; a : stratified log rank test

Overall Survival (OS) - Per protocol population

Median OS for per protocol analysis was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm. The risk of death is reduced by 25% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.75 (95% CI: 0.59; 0.96 p=0.0197). In a subsequent update, OS in the per protocol patient population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus 4.3 months), with a reduction of risk of death by 26% HR 0.74 (95% CI: 0.59, 0.94). This difference was statistically significant (p = 0.0130).

Figure 3. Overall survival: Per protocol population



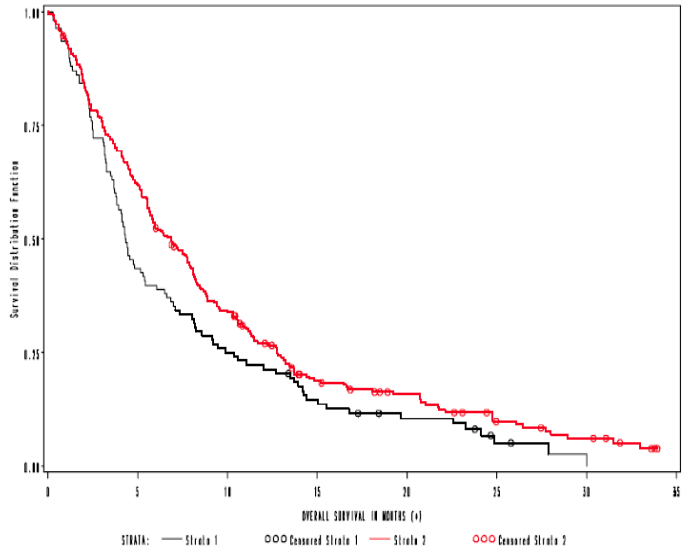
	VFL+BSC (N=244)	BSC (N=107)
No. of events	216	102
No of censored (%)	28 (11.5)	5 (4.7)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
Hazard ratio (95% CI)	0.74 (0.59, 0.94)	
p value[a]	0.0130	

Overall Survival (OS) - Eligible patients

Median OS in the eligible population was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm. The risk of death is reduced by 22% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.78 (95%CI: 0.61, 0.99 p=0.0403). The OS difference between the 2 arms is now statistically significant.

In a subsequent analysis, OS in the eligible patient population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus 4.3 months), with a reduction of risk of death by 23% HR 0.77 (95% CI: 0.61, 0.98). This difference was statistically significant (p = 0.0320).

Figure 4. Overall survival: Eligible population

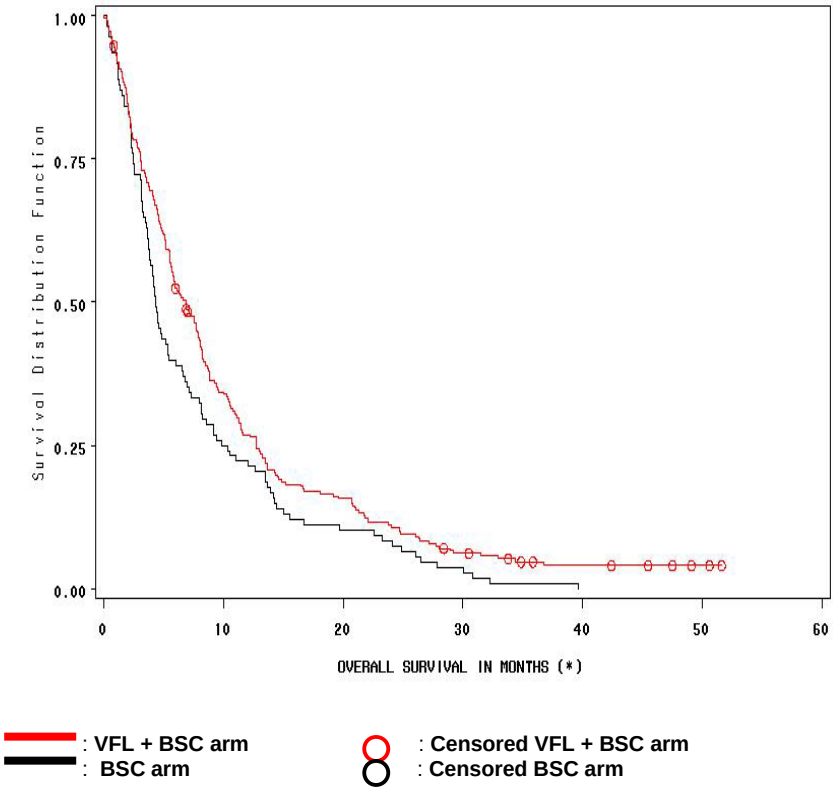


	VFL+BSC (N=249)	BSC (N=108)
No. of events	220	102
No of censored (%)	29 (11.7)	6 (5.6)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
Hazard ratio (95% CI)	0.77 (0.61, 0.98)	
p value[a]	0.0320	

CSR VFL 302 Additional efficacy analysis Table 12; a : stratified log rank test

The overall survival updated on November 30th 2008 still confirmed the previous reported data of 2 months median survival advantage favouring VFL+BSC with a reduction of risk of death of 22% [HR (95% CI): 0.78 (0.61-0.96)], this difference being statistically significant (p=0.0227)

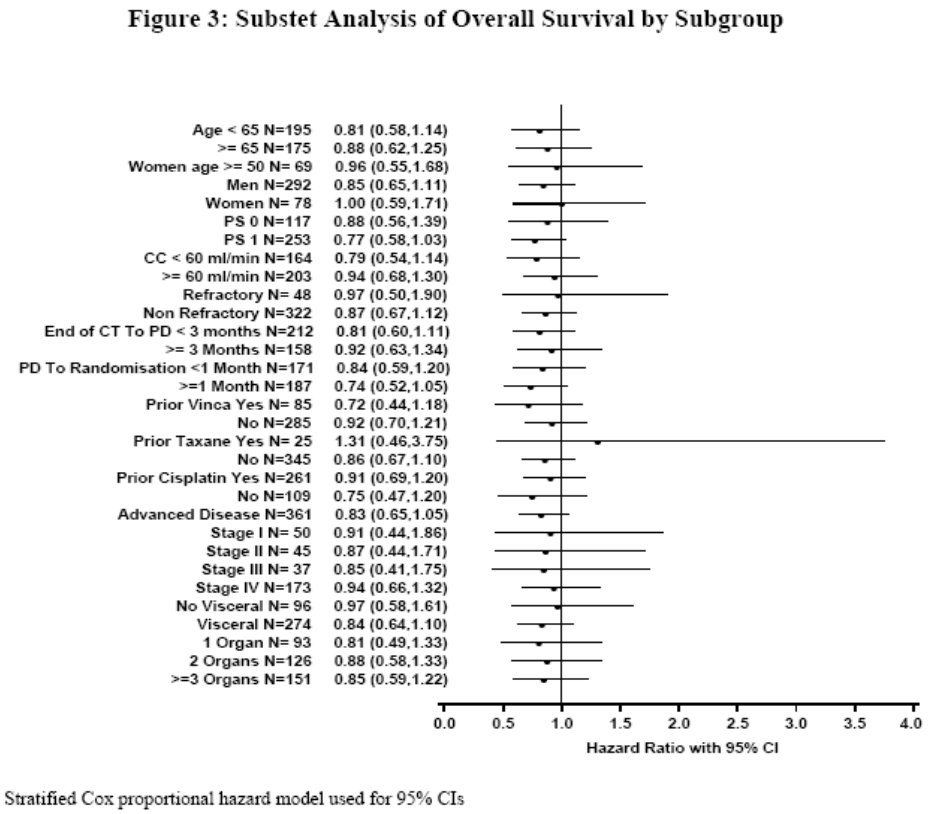
Figure 5: Overall survival: Eligible population (Cut-off : Nov 30th, 2008)



Overall Survival by Subgroups

For the majority of subsets, overall survival was longer for the vinflunine arm compared with the BSC arm (HR < 0.95). See figure below.

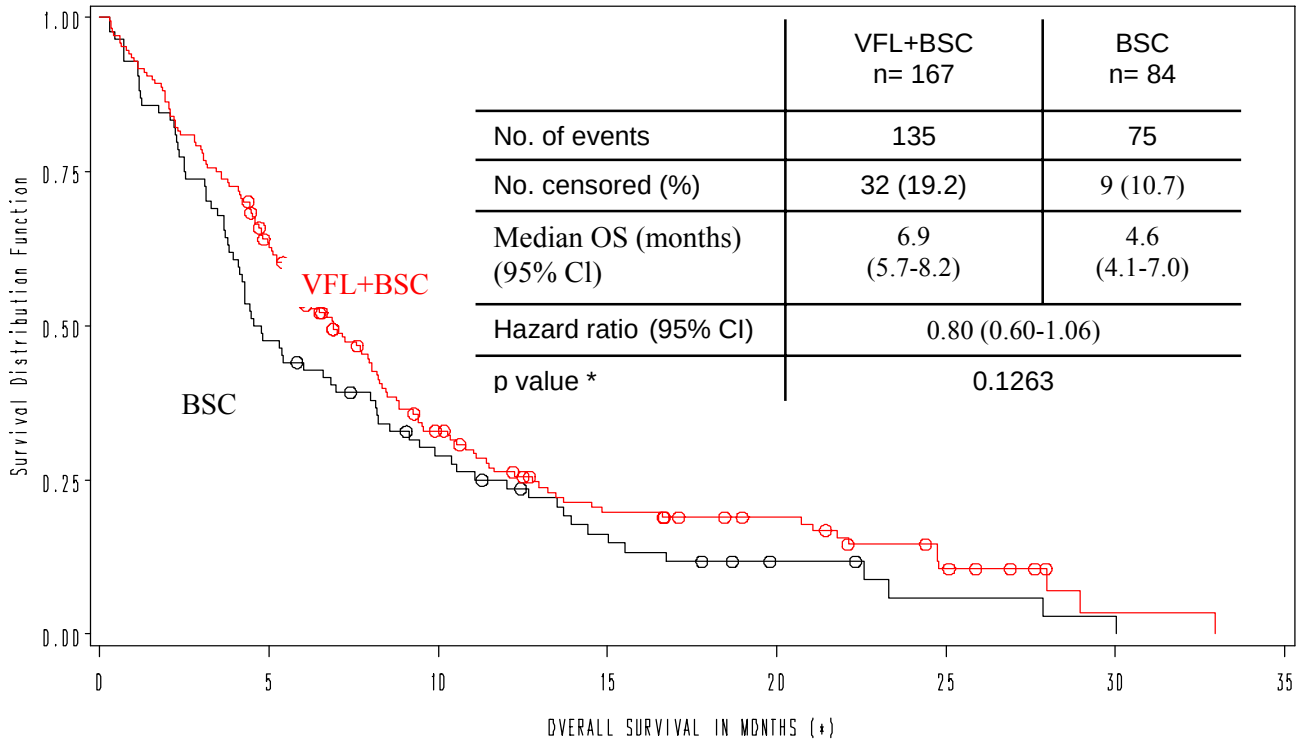
Figure 6. Subset Analysis of Overall Survival by Groups



Stratified Cox proportional hazard model used for 95% CIs

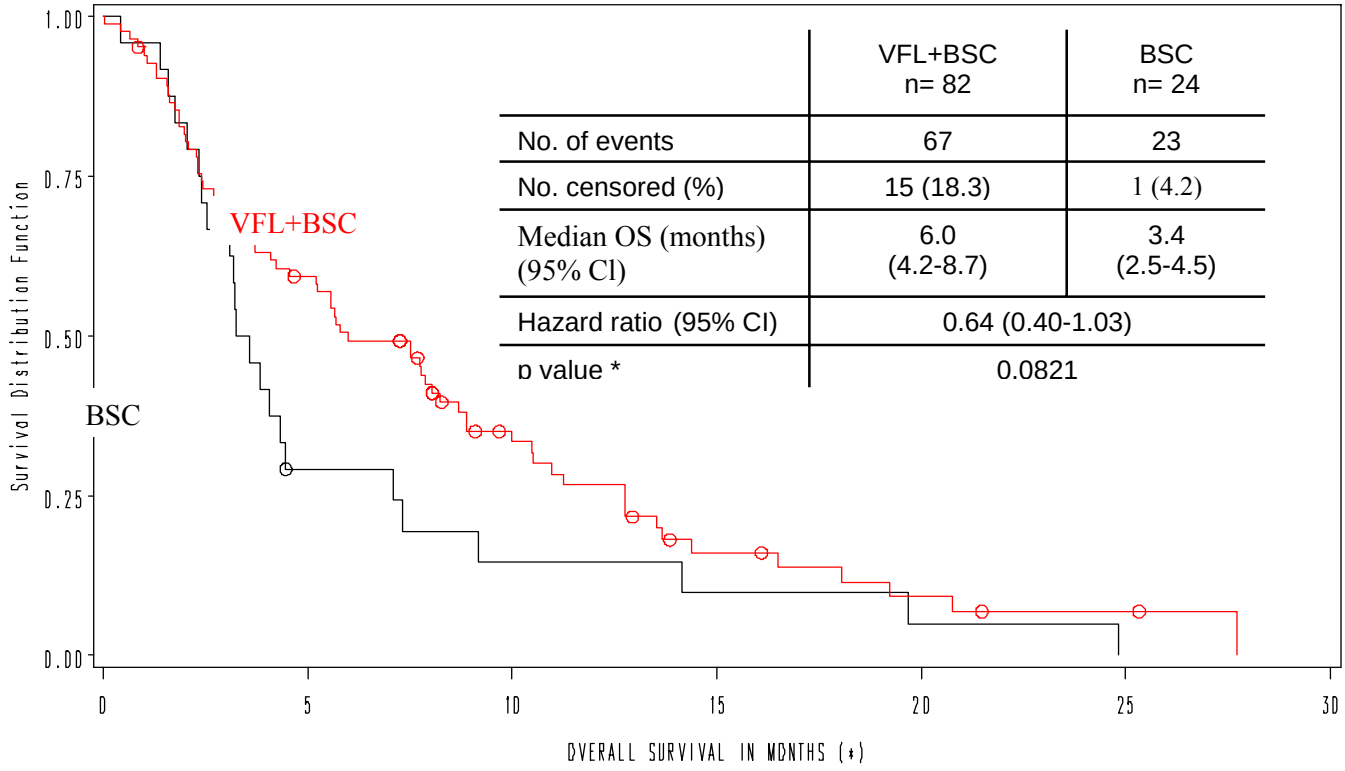
Overall Survival –Prior Platinum therapy – Eligible Population.

Figure 7. Overall Survival in patients with prior cisplatin therapy



	VFL+BSC n= 167	BSC n= 84
No. of events	135	75
No. censored (%)	32 (19.2)	9 (10.7)
Median OS (months) (95% CI)	6.9 (5.7-8.2)	4.6 (4.1-7.0)
Hazard ratio (95% CI)	0.80 (0.60-1.06)	
p value *	0.1263	

Figure 8. Overall Survival in patients without prior cisplatin therapy.



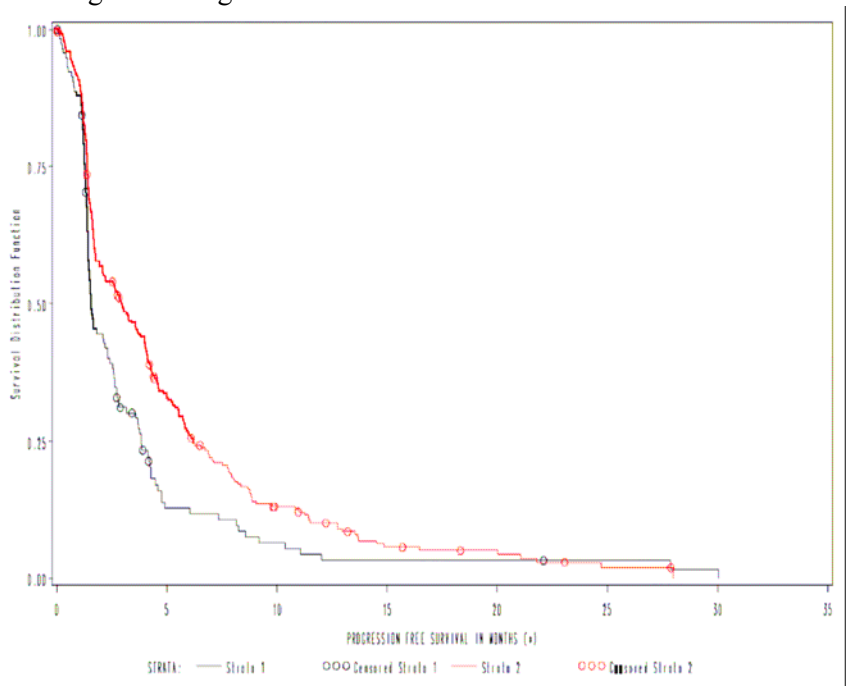
	VFL+BSC n= 82	BSC n= 24
No. of events	67	23
No. censored (%)	15 (18.3)	1 (4.2)
Median OS (months) (95% CI)	6.0 (4.2-8.7)	3.4 (2.5-4.5)
Hazard ratio (95% CI)	0.64 (0.40-1.03)	
p value *	0.0821	

Secondary Endpoints

Progression free survival - All Randomised Patients

Following IRC assessment of the randomised population, PFS was 3.0 months (2.1, 4.0) in the vinflunine + BSC group and 1.5 (1.4, 2.3) in the BSC arm [p = 0.0012]. By investigator, PFS was 2.8 months in the vinflunine + BSC group compared to 1.4 months in the BSC arm (p < 0.0001).

Figure 9. Progression free survival - All Randomised Patients

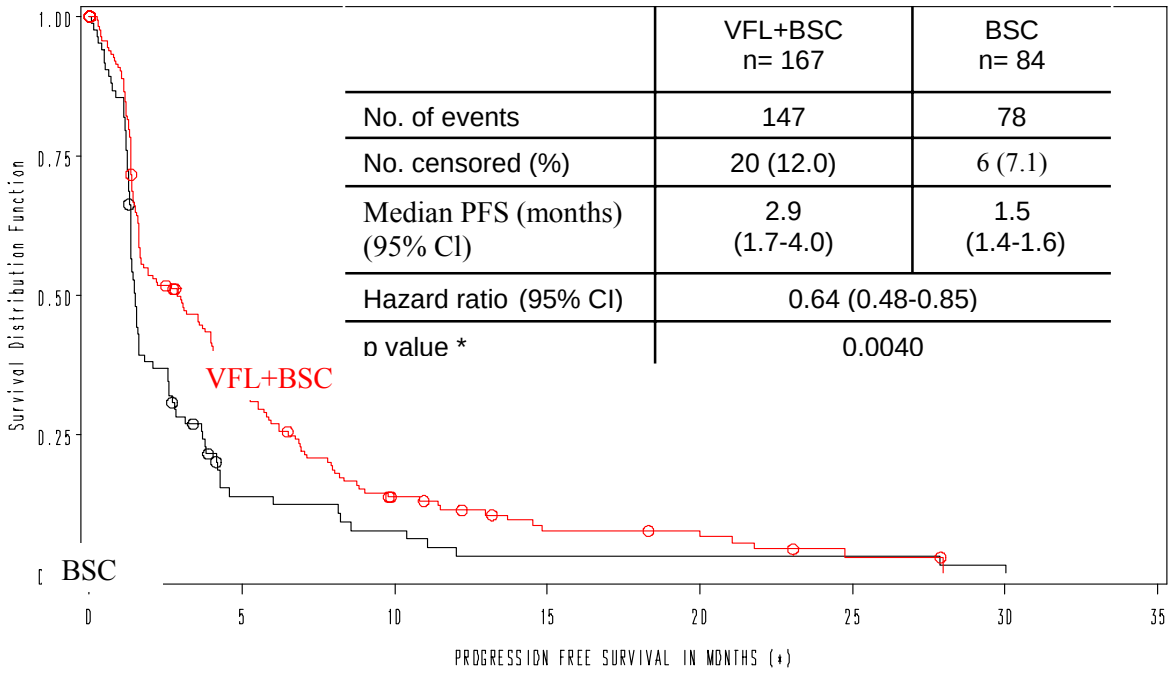


	VFL+BSC (N=253)	BSC (N=117)
No. of events	228	107
No. censored (%)	25 (9.9)	10 (8.6)
PFS in months		
Median (95% CI)	3.0 (2.1, 4.0)	1.5 (1.4, 2.3)
Hazard ratio (95% CI)	0.68 (0.54, 0.86)	
p value[a]	< 0.0012	

Progression-free Survival (months) all randomised	**VFL + BSC**	**BSC**
Investigator	**N= 253**	**N= 117**
Median (95 % CI)	2.8 (2.4, 3.4)	1.4 (1.4, 1.5)
Hazard ratio (95% CI)	0.58 (0.47, 0.73)	
P value	< 0.0001	
IRC	**N=253**	**N=117**
Median (95 % CI)	3.0 (2.1, 4.0)	1.5 (1.4, 2.3)
Hazard ratio (95% CI)	0.68 (0.54, 0.86)	
P value	= 0.0012	

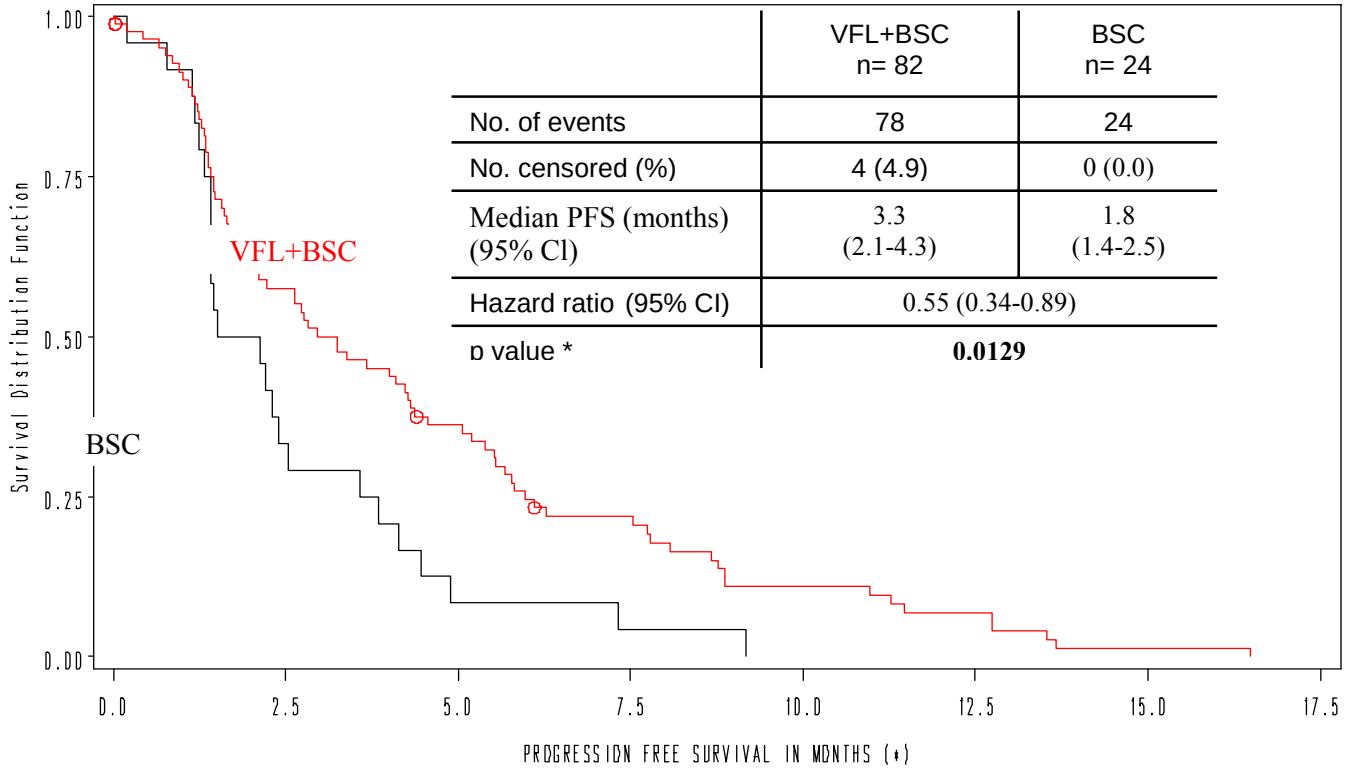
Progression-Free Survival – Prior platinum therapy – Eligible Population

Figure 10. Progression-Free Survival in patients with prior ciplatin



	VFL+BSC n= 167	BSC n= 84
No. of events	147	78
No. censored (%)	20 (12.0)	6 (7.1)
Median PFS (months) (95% Cl)	2.9 (1.7-4.0)	1.5 (1.4-1.6)
Hazard ratio (95% CI)	0.64 (0.48-0.85)	
p value *	0.0040	

Figure 11. Progression-Free Survival in patients without prior cisplatin



	VFL+BSC n= 82	BSC n= 24
No. of events	78	24
No. censored (%)	4 (4.9)	0 (0.0)
Median PFS (months) (95% CI)	3.3 (2.1-4.3)	1.8 (1.4-2.5)
Hazard ratio (95% CI)	0.55 (0.34-0.89)	
p value *	**0.0129**	

Tumour Response rate

The IRC evaluated study-related images and a subset of selected, prospectively defined clinical information for all patients who were randomised. The reviewers conducted response determination using RECIST for each patient. The on-study best overall response was calculated to 30th November, 2006 and to 31st May, 2007. IRC information was also used to compare the response rate, to compare disease control rate, duration of response, time to response and duration of disease control.

The response rate (RR) in all 253 randomised patients, as assessed by IRC was 6.3% (95% CI: 3.7 - 10.1) and the RR as assessed by investigators was 11.1% (95% CI: 7.5 - 15.6). Based on IRC assessment, the response rate in evaluable patients was 8.6% (95% CI: 5.0 - 13.7) in the vinflunine + BSC and 0% in the BSC arms. The median time from randomisation to first response in the randomised population for the vinflunine + BSC group was 2.1 months and the median duration of response was 7.4 months. The median duration of stabilisation in the randomised population was 5.4 months in the vinflunine + BSC group and 4.2 months in the BSC group.

Table 22 Response Rates - Evaluable Patients

Response Rates: Evaluable Patients	**VFL + BSC**	**BSC**
Investigator Best Overall Response, N (%)	**N= 215**	**N= 93**
CR	0 (0)	0 (0)
PR	28 (13.0)	0 (0)
SD	106 (49.3)	21 (22.6)
PD	81 (37.7)	72 (77.4)
ORR, % (95% CI)	13.0 (8.8, 18.3)	0 (0)
IRC Best Overall Response, N (%)	**N= 185**	**N= 85**
CR	0 (0)	0 (0)
PR	16 (8.6)	0 (0)
SD	86 (46.5)	23 (27.1)
PD	83 (44.9)	62 (72.9)
ORR, % (95% CI)	8.6 (5.0, 13.7)	0 (0)

Disease Control/Rate (DC/R)

Disease control is defined as: DC = PR + SD. Based on IRC assessment, the disease control rate for all randomised patients was 41.1% in the vinflunine + BSC group versus 24.8% in the BSC group [p = 0.0024]. Duration of DC, in all randomised patients was 5.7 months in the vinflunine + BSC group versus 4.2 months in the BSC only arm. The disease control rate in evaluable patients was 55.1% in the vinflunine + BSC group versus 27.1% in the BSC group [p < 0.0001].

Table 23. Disease Control Rate – All Randomised Patients

	VFL + BSC	**BSC**
Disease Control All Randomised patients (investigators)	**N= 253**	**N= 117**
DCR (95% CI)	53.8 (47.4, 60.0)	22.2 (15.1, 30.8)
P-value	< 0.0001	
Disease control All Randomised patients (IRC)	**N=185**	**N=85**
DCR (95%CI)	41.1 (35.0, 47.4)	24.8 (17.3, 33.6)
P-value	= 0.0024	
Duration of disease control (investigator)- Randomised patients	**N= 253**	**N= 117**
Median (months) (95% CI)	5.4 (4.6, 5.9)	4.2 (3.0, 5.0)
Duration of disease control - (IRC) Randomised patients	**N=253**	**N=117**
Median (months) (95% CI)	5.7 (5.0,6.3)	4.2 (3.8,4.9)

Quality of life

The EORTC QLQ-C30 was completed at baseline, at the end of cycles 1, 2, 4, and 6 for the vinflunine + BSC arm and at baseline, Days 21, 42, 84 and 126 for the BSC arm. Compliance at baseline was 91.3% in the vinflunine + BSC arm and 90.6% in the BSC arm. Compliance at the end of cycle 6/Day 126 was 58.4% in the vinflunine + BSC arm and 53.7% in the BSC arm. There was no statistically significant difference between the groups in change from baseline of the EORTC QLQ-C30 global health status score (p=0.658).

Clinical Benefit

The clinical benefit parameter is a composite endpoint taking into account the following clinical parameters assessed at the time of randomisation and every cycle/21 days: PS (WHO Scale), weight and pain intensity (measured by the McGill-Merlzack Pain Questionnaire) and incidence of palliative radiotherapy.

The clinical benefit response rate in the evaluable population was 9.4% in the vinflunine + BSC arm and 7.6% in the BSC arm (p = 0.6066). There was no statistically significant difference between the two arms in terms of clinical benefit response rate.

Palliative Radiotherapy

Administration of at least one course of palliative radiotherapy was statistically significantly higher in the BSC arm (23.9%) compared to the vinflunine + BSC arm (4.0%).

Ancillary analyses

Multivariate Analysis of OS using a Cox proportional hazard model

Baseline patient characteristics were imbalanced between the 2 treatment arms for WHO PS ≥ 1 (vinflunine + BSC arm (71.5%) BSC arm (61.5%). The sensitivity analyses of the primary endpoint were performed on the whole randomised population, using the Cox proportional hazard model adjusted for the stepwise selected covariates pre-specified in the protocol and the Statistical Analysis Plan (treatment group, alkaline phosphatase, haemoglobin, visceral metastases, ECOG Performance Status, and pelvic irradiation). In the multivariate analysis of OS, including pre-specified prognostic factors, Performance Status (PS 0 versus 1) was the most important prognostic factor with a HR of

0.48 (p<0.0001). Based on the results of this model, vinflunine reduced the risk of death by 23% compared with BSC only, with a hazard ratio HR of 0.77 (95% CI: 0.61 - 0.98, p = 0.0360).

Table 24: Multivariate Analysis of Overall Survival Using a Cox Proportional Hazard Model: All Randomised Patients

Variables at Randomisation [a]	Hazard Ratio (95% CI)	p Value[b]
Treatment group	0.772 (0.61, 0.98)	0.0360
Alkaline phosphatase	0.624 (0.50, 0.79)	< 0.0001
Haemoglobin	0.660 (0.52, 0.84)	0.0007
Visceral involvement	0.635 (0.48, 0.84)	0.0013
WHO performance status	0.482 (0.37, 0.63)	< 0.0001
Pelvic irradiation	0.742 (0.56, 0.99)	0.0425

a: This analysis used the following prognostic factors (at baseline): treatment group, alkaline phosphatase (< median, ≥ median), haemoglobin (< median, ≥ median), visceral metastases (yes, no), WHO PS (0, ≥ 1), radiotherapy of the pelvis (yes, no), and the presence of lymph nodes (yes, no). b: Wald Chi square test
CSR VFL 302 Table 37

An additional multivariate analysis of overall survival using a Cox proportional hazard model was also conducted in the eligible (modified ITT) population and showed a statistically significant effect of the treatment arm on survival (p=0.0027) (see table below).

Table 25: Multivariate Analysis of Overall Survival Using a Cox Proportional Hazard Model Stratified on Refractory Status: Eligible Population

Variables at Randomisation [a]	Hazard Ratio (95% CI)	p Value[b]
Treatment group	0.686 (0.54, 0.88)	0.0027
Alkaline phosphatase	0.655 (0.52, 0.83)	0.0004
Haemoglobin	0.610 (0.48, 0.78)	<0.0001
Visceral involvement	0.710 (0.54, 0.94)	0.0163
WHO performance status	0.470 (0.36, 0.62)	<0.0001
Pelvic irradiation	0.686 (0.51, 0.92)	0.0123

a: This analysis used the following prognostic factors (at baseline): treatment group, alkaline phosphatase (< median, ≥ median), haemoglobin (< median, ≥ median), visceral metastases (yes, no), WHO PS (0, ≥ 1), radiotherapy of the pelvis (yes, no).
b: Wald Chi square test

The results observed in the ITT population were confirmed by those observed in the eligible population.

The Cox model proportional hazards assumption was investigated with the test of Grambsch and Therneau as performed for the Cox model in the ITT population. The global test did not show a deviance from the proportional hazards assumption (p=0.273). Taken individually, only the Performance Status showed evidence of deviation from the proportional hazards assumption (p=0.028). Thus, the Cox model was performed stratifying by Performance Status. The results are given in the table below.

Table 26: Multivariate Analysis of Overall Survival Using a Cox Proportional Hazard Model Stratified on Refractory Status and PS : Eligible Population

Variables at Randomisation [a]	Hazard Ratio (95% CI)	p Value[b]
Treatment group	0.708 (0.55, 0.91)	0.0067

Variables at Randomisation [a]	Hazard Ratio (95% CI)	p Value[b]
Alkaline phosphatase	0.664 (0.52, 0.84)	0.0007
Haemoglobin	0.625 (0.49, 0.80)	0.0002
Visceral involvement	0.720 (0.54, 0.95)	0.0224
Pelvic irradiation	0.695 (0.52, 0.93)	0.0160

a: This analysis used the following prognostic factors (at baseline): treatment group, alkaline phosphatase (< median, ≥ median), haemoglobin (< median, ≥ median), visceral metastases (yes, no), Refractory status (Refractory, non refractory), radiotherapy of the pelvis (yes, no).

b: Wald Chi square test

The proportional hazards assumption was tested in the model stratified on the PS, and neither the global test (p=0.731) nor the individual tests (all p-values above 0.05) showed a deviance from the assumption.

No effect of prior cisplatin (p=0.4626) nor interaction with the treatment group (p=0.5825) can be evidenced with the multivariate Cox analysis (Table 27) leading to the conclusion that the multivariate model to be analyzed in the eligible population is the one without the cisplatin covariate. In this analysis (Table 28), it is found that VFL improves significantly the Overall Survival of the patients (HR: 0.686 (0.536, 0.877), p-value: 0. 0027).

Table 27: Multivariate Analysis of Overall Survival Using a Cox Proportional Hazard - Eligible Population

Variables at Randomisation	Hazard Ratio (95% CI)	p Value
Treatment group	0.606 (0.375, 0.979)	0.0407
Alkaline phosphatase	0.659 (0.520, 0.835)	0.0006
Haemoglobin	0.613 (0.480, 0.784)	<.0001
Visceral involvement	0.719 (0.542, 0.954)	0.0222
WHO performance status	0.358 (0.358, 0.622)	<.0001
Pelvic irradiation	0.680 (0.506, 0.915)	0.0108
Prior Cisplatin[a]	0.836 (0.518, 1.349)	0.4626
Prior Cisplatin * Treatment group	1.169 (0.670, 2.041)	0.5825

This leads to a treatment effect of HR (95% CI)=0.606 (0.375, 0.979) in the absence of prior cisplatin and of HR (95% CI)=0.708 (0.532, 0.944) in the presence of prior cisplatin.

Table 28: Multivariate Analysis of Overall Survival Using a Cox Proportional Hazard - Eligible Population

Variables at Randomisation	Hazard Ratio (95% CI)	p Value
Treatment group	0.686 (0.536, 0.877)	0.0027
Alkaline phosphatase	0.655 (0.518, 0.829)	0.0004
Haemoglobin	0.610 (0.477, 0.780)	<.0001
Visceral involvement	0.710 (0.536, 0.939)	0.0163
WHO performance status	0.470 (0.357, 0.619)	<.0001
Pelvic irradiation	0.686 (0.511, 0.922)	0.0123

Multivariate Analysis of PFS using a Cox proportional hazard model – Eligible Population

No effect of prior cisplatin (p=0.8039) and no interaction between treatment group and prior cisplatin (p=0.9716). The pre-specified multivariate Cox model in the eligible population was used in order to adjust the effect of the treatment group on the prognostic factors when analyzing the PFS. In this model, the effect of the treatment group is found to be significant (p=0.0001).

Table 29: Multivariate Analysis of Progression free Survival Using a Cox Proportional Hazard - Eligible Population

Variables at Randomisation	Hazard Ratio (95% CI)	p Value
Treatment group	0.625 (0.390, 1.001)	0. 0503
Alkaline phosphatase	0.779 (0.622, 0. 976)	0. 0299
Haemoglobin	0.715 (0.568, 0. 900)	0. 0043
Visceral involvement	0.698 (0.530, 0. 921)	0. 0110
WHO performance status	0.720 (0.558, 0. 930)	0.0117
Pelvic irradiation	0.687 (0.520, 0. 906)	0. 0080
Prior Cisplatin[a]	1.062 (0.663, 1.700)	0. 8039
Prior Cisplatin * Treatment group	1.010 (0.587, 1.739)	0. 9716

This leads to a treatment effect of HR (95% CI)=0.625 (0.390, 1.001) in the absence of prior cisplatin and of HR (95% CI)=0.631 (0.476, 0.836) in the presence of cisplatin.

- Clinical studies in special populations

Renal Impairment

A pharmacokinetic study of IV vinflunine in cancer patients with renal impairment was conducted and is still ongoing (CSR L0070 IN 113 interim). The trial is an open-label, non-randomised, multicentre PK Phase I study in patients with varying degrees of renal impairment. The primary objective of the study was to investigate the effect of renal impairment on the PK of vinflunine and DVFL in adult cancer patients with varying degrees of renal dysfunction and, to propose a dose adjustment when required. The secondary objectives were to assess the safety of vinflunine. The results of the interim analysis suggested that Clcr of vinflunine was decreased in patients with renal impairment. The decrease was of approximately 16% in patients with moderate renal impairment and of approximately 30% in patients with severe renal impairment. Renal impairment affected the elimination of both vinflunine and DVFL to a similar extent.

Hepatic Impairment

A phase I pharmacokinetic dose adjusted of IV vinflunine in cancer patients with liver dysfunction was conducted during the drug development (CSR L0070 IN 104). The study was an open-label multicentre phase I study. The primary objective of the study was to determine the Recommended Dose (RD) of vinflunine and to investigate the pharmacokinetics and tolerability of vinflunine in cancer patients with varying degrees of hepatic dysfunction. The secondary objectives were to recommend dose adjustments of vinflunine if needed.

For pharmacokinetic analysis, no statistical difference was evidenced for VFL and DVFL among the 3 groups of liver impairment and between liver impairment groups and the control group (n= 49). No significant correlation was observed between individual values of VFL clearance and each biological variables at baseline (i.e bilirubin, SGOT, SGPT, ALP, GGT, total plasma protein and prothrombine time) and between VFL clearance and the presence or absence of cirrhosis.

The liver impairment (LI) effect was also studied in the population PK analysis (372 patients including LI patients data) which showed that covariates such as total bilirubin, transaminases and alkaline phosphatase were not related to VFL Cltot. Likewise, the population PK approach did not show any modification of VFL Cltot in patients with liver metastases (n= 141 patients out of 372).

Elderly Patients
A pharmacokinetic study of IV vinflunine in elderly cancer patients (L00070 IN 114) started in January 2005 and is still ongoing.

- Supportive study(ies)

Phase II study - VFL 202
This was an open-label, multi-centre (18 centres in 5 European countries), single-arm non-randomised Phase II study of vinflunine. Patients with TCCU who had relapsed after a previous platinum-containing regimen were enrolled. The study was carried out between November 2000 and September 2002. The primary objective was to estimate the response rate according to modified WHO criteria. Secondary objectives were to assess the duration of response, progression free survival and overall survival and to evaluate the qualitative and quantitative toxicities associated with the treatment. An independent radiologist reviewed all the responses and disease stabilisations lasting at least 2 consecutive assessments. Tumour assessment was performed every two cycles. Subjects included Men or women > 18 years, who had histologically proven advanced TCCU of the bladder, with documented relapse or progression after first-line platinum-containing chemotherapy and KPS > 80. The median age of patients treated with 350 mg/m² group was 66 and the median age of patients treated with 320 mg/m² group was 63. Previous first-line chemotherapy included cisplatin-vinblastine (43%) and gemcitabine /platinum (49%). 51% of patients had progressed within 6 months of their prior chemotherapy.

Vinflunine was administered as a 10-minute infusion at 350 mg/m² every 3 weeks for the first 6 patients. For the 51 subsequent patients, vinflunine was administered at 320 mg/m² every 3 weeks following preliminary safety evaluation. The treatment was discontinued in case of progressive disease, unacceptable toxicity, intercurrent illness or other reactions which in the judgement of the investigator, affected clinical status of the patient or request by the patient to withdraw.

51 patients were treated at 320 mg/m², Day 1 every three weeks. Out of 47 evaluable patients, the overall response rate was 17.6% (95% CI: 7.7-30.8%) as assessed by independent review and the median duration of the response was 9.1 months, with a 95% confidence interval ranging from 4.2 to 15.0 months. The median progression-free survival calculated was 3 months [95% CI: 2.4-3.8 months], while the median overall survival was 6.6 months [95% CI: 4.8-7.6 months]

Safety conclusions refer solely to the patients treated at the dose of 320 mg/m². In terms of drug exposure, the relative dose intensity was 95.5% [range: 71.0 - 102.3%]. The majority of dose reductions were due to non-haematological toxicities (280 mg/m² [9.6%]). Neutropenia was reported in 82.4% of patients with grade 3-4 severity in 66.7%. The neutrophil nadir appeared at a median day 12 [range: 3-21] and lasted a median of 7 days [range: 1-14]. Grade 3 and 4 febrile neutropenia were observed in 7.8% and 2.0% of patients. Three cases of septicaemia/severe neutropenia occurred, with a fatal outcome for 2 patients. The overall incidence of anaemia was in 90.2% of patients. Grade 3 anaemia occurred in 13.7% of patients (5.1% of cycles). A significant percentage of patients (66.7%) experienced fatigue of mild intensity. Grade 3 fatigue occurred in 9.8% of patients (3.0% of cycles) with no grade 4 fatigue being observed. Constipation appeared to be the most important non-haematological toxicity seen, with an overall incidence of 64.7% of patients. Four patients (7.9%) experienced severe (grade 3/4) constipation. All four patients had undergone significant prior abdominal surgery; three also received opioids + 5HT3 antagonists. Constipation was notified as a SAE in 7 patients. Grade 3 toxicities included neutropenia (33.3%), anaemia (16.7%), nausea and vomiting (16.7%). Grade 4 toxicities included leucopenia (50.0%), neutropenia (66.7%), anaemia (16.7%), one patients experienced a fatal febrile neutropenia, and three patients died due to SAE (septic shock, septicaemia febrile neutropenia).

Phase II study CA 001
This was an open-label, multi-centre (60 centres in 12 countries), single-arm, non-randomised Phase II study of vinflunine. Patients with TCCU who had relapsed after a previous platinum-containing regimen were enrolled. The Study was carried out between the 27th January 2005 and the 10th April

2007. The primary objective was to estimate the response rate (complete response [CR] + partial response [PR]; as defined by modified WHO criteria and determined by an Independent Response Review Committee (IRRC). Tumour assessment was performed every 6 weeks. Secondary objectives included estimation of the duration of response, time to response, disease control rate, progression free survival (PFS), and overall survival (OS) and to evaluate the safety profile of vinflunine and vinflunine pharmacokinetics. Inclusion criteria included men and women > age 18 years who had histologically proven locally advanced or metastatic TCCU, had documented progression up to 12 months after the last dose of a platinum-containing regimen, and KPS of 100, 90 or 80. The median age was 66 years (range: 31 to 83 years).

Vinflunine was administered every 21 days; prior to Amendment 5, patients received vinflunine at a dose of 320 mg/m² every 3 weeks if they had a KPS of 100 without prior pelvic irradiation. Upon implementation of Amendment 5, patients also needed to be < 75 years old and have a CrCl > 60 mL/min to receive vinflunine at a starting dose of 320 mg/m². Patients received vinflunine at an initial dose of 280 mg/m² if they had a KPS of 90 or 80

Among the 175 patients enrolled, 151 were treated with the study medication. In the All-Treated population, the primary endpoint of independently assessed response rate was 14.6% [95% CI: 9.4 - 21.2]. Duration of tumour responses was a median of 5.95 months (95% CI: 5.42 - 9.46). Median PFS was 2.76 (95% CI: 2.56 - 3.84) and median OS was 7.89 months (95% CI: 6.67 - 9.69)

The most frequent adverse events noted were myelosuppression, constipation and fatigue. Myelosuppression was common. Severe (Grade 3-4) events of neutropenia and leukopenia were reported in more than half of all patients. Febrile neutropenia was uncommon (6.6%). The most common non-haematologic AEs were constipation, followed by fatigue, nausea, weight decrease, anorexia, diarrhoea, vomiting, abdominal pain, alopecia, and back pain. The most common (> 10%) non-haematologic severe (Grade 3-4) AEs were constipation and fatigue. The frequency of discontinuation due to treatment related AEs was 15%. The incidence of peripheral neuropathy was low and only 1 Grade 3 event was reported. Other AEs of special interest (ileus, intestinal obstruction, abdominal pain, injection/infusion site reactions, immediate hypersensitivity, extravastion, cardiac arrhythmias, nausea, vomiting, stomatitis/mucositis, infection with severe neutropenia, and diarrhoea) were manageable, though a few of these AEs led to discontinuation. 86 (57%) patients died after the study started, 10 of these (7%) died within 30 days of their last vinflunine dose. 2 patients (1%) died due to events judged to be related to the study drug (neutropenic sepsis, myocardial infarction).

- Discussion on clinical efficacy

Overall, the efficacy results were considered to be consistent and the efficacy endpoint of overall survival was considered to be significantly different between the two treatment groups, based on a consistent picture across a number of secondary analyses including the eligible population analysis and following adjustment for covariates. Secondary endpoints, particularly progression-free survival, favoured the vinflunine arm, supporting the conclusion that the product is efficacious. The effects were consistent across subgroups. The updated overall survival data, at two years confirmed the positive treatment effect of vinflunine on overall survival as reported at the first cut-off date (Nov 30th, 2006).
With regards to potential interactions between treatment effect and prior cisplatin therapy in the eligible population, the results were better in those patients without prior cisplatin therapy, but there was still evidence of efficacy in the group of patients who had received prior cisplatin therapy. A favourable trend was observed with the log-rank test and when covariates were adjusted in the Cox regression model, the difference reached statistical significance in both subgroups.

The following major objections were raised regarding the clinical efficacy data submitted.

1. The CHMP was initially of the opinion that insufficient evidence for efficacy of Vinfluinine had been provided. The primary analysis from the single pivotal study had failed to show a statistical significant difference in overall survival for vinflunine when compared to BSC in the ITT (intention to

treat) population. A difference in overall survival was only observed in secondary analyses, excluding patients from the ITT population. The need to exclude a substantial proportion of subjects from the per protocol analysis cast some doubt on the overall validity of the trial. Potential biases arising from these specific exclusions, needed to be addressed.

In the dossier submitted, the eligible population corresponds to the whole randomised population minus the ineligible patients. The Applicant argued that the eligible patients represent the actual TCCU population targeted by the protocol. In the eligible population, a median of 2 months survival advantage favouring the VFL+BSC arm was observed (6.9 months vs. 4.3 months). A statistically significant (stratified log-rank test) survival difference between the 2 arms was achieved (HR 0.78 [0.61, 0.99] p=0.0403). In this analysis, where patients with clinically significant protocol violations at baseline (i.e. those violating the inclusion criteria) were excluded, the results did achieve statistical significance.

The primary analysis performed in the ITT population was affected by the higher proportion of non eligible patients in the BSC arm (9 non eligible patients for BSC vs. 4 for VFL + BSC). Ineligible patients included patients with no progression to first line platinum-containing chemotherapy for advanced disease (12 out of 13 patients) or patients with no advanced or metastatic histologically proven TCCU. This is consistent with the longer survival observed in these patients. Importantly, non eligible patients were identified using a blinded review before database lock, and all analyses were performed after the database lock (30th March 2007). These patients are not representative of the population targeted by the protocol (advanced TCCU that has failed prior platinum-containing regimen).

Furthermore, a significant treatment effect of vinflunine (p=0.036) on overall survival in the pre-specified multivariate Cox analysis conducted in the ITT population was seen. Vinflunine reduced the risk of death by 23% compared to BSC with a hazard ratio of 0.77 (95% CI: 0.61-0.98). In addition, the fact that all other parameters that had a significant independent impact on OS in multivariate analysis (liver involvement, number of organs involved, alkaline phosphatase, haemoglobin, PS and pelvic irradiation) were the same in the three populations analysed (ITT, eligible and Per-Protocol) further supports the consistency of the results.

Therefore the CHMP considered that:

a. The primary analysis from the single pivotal study failed to show a statistical significant difference in overall survival for vinflunine when compared to BSC in the ITT population.

b. A statistically significant effect on overall survival was obtained from the pre-specified multivariate Cox analysis. The hazard ratio from this analysis was 0.77 (0.61, 0.98), very consistent with the 0.78 (0.61, 0.99) obtained from the eligible population analysis. At the request of the CHMP, the Applicant repeated the analysis stratifying for Performance Status and thereby not relying on proportional hazards for this covariate. The results were consistent with those previously observed - ITT population (p=0.0420, HR 0.776 (0.61, 0.99)); eligible population (p=0.0067, HR=0.708 (0.55, 0.91)).

2. The Applicant was also asked to present efficacy results in relation to prior platinum based therapy. Based on the evidence provided, the results were better in the 'without prior cisplatin therapy group', although evidence of efficacy was still seen in the 'prior cisplatin group'. None of the prior platinum regimens received by the patients appeared to have a significant interaction with vinflunine on OS, PFS and DCR and the effect of the treatment arm was still found to be significant when adjusted for prior platinum based therapies. Therefore, the CHMP agreed to modify section 5.1 of the SPC to include the following wording:

In the two multi-centre open-label, single-arm phase II clinical trials a total of 202 patients were treated with vinflunine.

In the multi-centre, open-label controlled phase III clinical trial, 253 patients were randomised to treatment with vinflunine + BSC (best supportive care) and 117 patients to the BSC arm.

The median overall survival was 6.9 months (vinflunine + BSC) vs. 4.6 months (BSC), but the difference did not reach statistical significance; hazard ratio 0.88 (95% CI 0.69,1.12). However a statistically significant effect was seen on progression-free survival. Median PFS was 3.0 months (vinflunine + BSC) vs 1.5 months (BSC) (p=0.0012).

In addition a pre-specified multivariate analysis performed on the ITT population demonstrated that vinflunine had a statistically significant treatment effect (p=0.036) on overall survival when prognostic factors (PS, visceral involvement, alkaline phosphatases, haemoglobin, pelvic irradiation) were taken into consideration; hazard ratio 0.77 (95% CI 0.61, 0.98). A statistically significant difference on overall survival (p=0.040) was also seen in the eligible population (which excluded 13 patients with clinically significant protocol violations at baseline who were not eligible for treatment); hazard ratio 0.78 (95% CI 0.61, 0.99). This is considered the most relevant population for the efficacy analysis, as it most closely reflects the population intended for treatment.

Efficacy was demonstrated in both patients with and without prior cisplatin use.

In the eligible population, the subgroup analyses according to the prior cisplatin use versus BSC on overall survival (OS) showed a HR (95% CI) = [0.64 (0.40 – 1.03); p=0.0821] in the absence of prior cisplatin, and a HR (95% CI) = [0.80 (0.60 – 1.06); p=0.1263] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of OS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.53 (0.32 – 0.88); p=0.0143] and a HR (95% CI) = [0.70 (0.53 – 0.94); p=0.0174], respectively.

In the subgroup analyses of prior cisplatin use versus BSC for progression free survival (PFS), the results were: HR (95% CI) = [0.55 (0.34 – 0.89); p=0.0129] in the absence of prior cisplatin, and a HR (95% CI) = [0.64 (0.48 – 0.85); p=0.0040] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of PFS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.51(0.31 – 0.86); p=0.0111] and a HR (95% CI) = [0.63(0.48 – 0.84); p=0.0016], respectively.

The CHMP was of the opinion that all these efficacy results, together with the acceptable and manageable safety of the drug demonstrated meaningful efficacy in the context of this patient group, with a short life expectancy and with an unmet medical need. Following the responses to both major objections, The CHMP considered that the Applicant had adequately demonstrated that the magnitude of the efficacy effects observed with vinflunine were comparable or greater than those observed and considered as clinically meaningful with other approved anticancer drugs in different and comparable settings. The meaningful efficacy effect was reinforced by the positive results of vinflunine across endpoints.

When consulted in this matter, the SAG-Oncology raised some concerns about the quality of the study (long duration of recruitment into the study, the large number of ineligible patients, the control arm not including other available options), that the claimed effects were not consistent across different endpoints as the response rate was low, and that the population studied was very heterogeneous concerning important prognostic factors for survival. The SAG agreed that the claimed difference in terms of overall survival would be clinically meaningful, provided that the claimed difference could be established using robust methodology. Although meaningful, the size of the effect on OS in the overall population was considered as modest. However, if efficacy were established based on robust methodology, the SAG stated that would be of interest to identify patients that might be more likely to benefit from this treatment. Currently, it was considered difficult to identify such population.

In addition, the CHMP raised other concerns with regards to the clinical efficacy data submitted in this dossier.

3. The applicant was asked to provide further discussion on the efficacy results of the Phase II studies in reference to available historical controls for TCCU patients. In the responses, the literature review demonstrates that when compared to other anti-cancer agents in patients with TCCU, VFL had

favourable activity. The data were considered to support the rationale for further study of vinflunine in the proposed indication.

4. The study Ca 183002 was prematurely terminated due to unexplained reasons. The clinical report of this study was submitted in the initial application and was requested by the CHMP, in particular, the reasons that led to study early termination, as these may include efficacy or safety issues that may be absolutely relevant to the present application. In the applicant's responses, the reasons for early Ca 183002 study termination were explained and the clinical report of this study was provided. Early termination of this study was due to commercial and development priorities matters and not to any major safety or efficacy issues related to vinflunine therapy.

5. The applicant was asked to submit data on the number of trial subjects in each arm who post-progression received chemotherapy, indicating what the type of chemotherapy was administered. The proportion of patients receiving chemotherapy at disease progression was well balanced between study arms, with slightly higher figures as expected among patients allocated to BSC (34.2%) than among VFL treated patients (28.8%). Of them, the percentage of patients that received multiple agents at disease progression was 62.5% (BSC arm) versus 57.5% (VFL arm). Therefore, an unbalanced distribution of further subsequent therapies among study arms was considered unlikely to have had a major impact in the ability to observe a survival benefit for VFL treated patients. In addition, data submitted suggests that vinflunine therapy does not compromise the ability to receive further treatment.

6. In line with the appendix on methodological issues on PFS in the CHMP anticancer guideline, the CHMP requested that the applicant address sensitivity analyses and discuss how ascertainment bias can be ruled out for the PFS results submitted. From the applicant's responses, all the efficacy assessments were reviewed by a blinded Independent Review Committee and the time interval between tumour assessments was descriptively investigated. This was shown to be balanced between the study arms. The applicant carried out PFS sensitivity analyses in order to confirm the consistency of the initial results. Sensitivity analyses of PFS showed consistency, confirming the benefit of VFL + BSC treatment.

7. The CHMP considered that the statistically significant improvement in progression free survival obtained was small and clinically marginal. The applicant was therefore asked to explain any relating clinical relevance. In its responses, the applicant demonstrated that TCCU patients perform favourably in terms of PFS when compared to historical controls. In the context of wider clinical practice, to support the claim of clinical relevance, the size of increase in PFS is similar to other licensed anti-cancer agents in comparable situations.

8. The demographic baseline characteristics in VFL 302 showed overall comparability in many aspects. Nevertheless the number of patients with disease stage unknown was considerably higher in the active treatment arm (14.6%) vs the BSC control arm: (7.7%). Since the disease of stage is related to survival prognosis, unfamiliarity with this important aspect may induce considerable bias. The CHMP recommended that a sensitivity analysis would reveal the impact of these cases with unknown stage of disease. The additional analysis supplied by the applicant demonstrated that the benefit in terms of overall survival of the VFL + BSC group compared with the BSC group was not due to the effect of disease stage at diagnosis. In terms of overall survival in the ITT population, when adjusted for the effects of potential prognostic factors including disease stage at diagnosis, the effect of the treatment arm was significant (p= 0.0221), showing a reduction of risk of death of 26% for the VFL + BSC group compared with the BSC group.

9. The CHMP considered that the study population was not representative for the patient in daily practice with advanced urothelial cancer progressive after first line chemotherapy as only Performance Status 0-1 patients were included, whereas the majority of patients have a poor Performance Status of 2 in whom any benefit of systemic therapy will be lower. Given that only patients with PS 0 and 1 were included in the phase III trial, which may not reflect the overall population of the patients with advanced TTCU relapsing after a platinum-containing regimen, the SPC was amended to reflect the

following statement in section 4.1: "Efficacy and safety of vinflunine has not been studied in patients with Performance Status ≥2".

Clinical safety

- Patient exposure

A total of 1203 patients received 4617 cycles of vinflunine as a single agent, either in the TCCU indication (450 patients) or in Non-TCCU setting. Safety analyses included all subjects who received at least one dose of study medication. 1202 cycles were administered in the 320 mg/m² group, with a median number of cycles delivered of 4 (range 1-21). 620 cycles were administered in the 280 mg/m² group, with a median number of cycles delivered of 2 (range 1-20).

Table 30. Vinflunine cumulative dose, dose intensity and relative dose intensity per patient

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose (mg/m²)	**320**	**320**	**280**	**All**	**320**	**280**	**All**	**320**	**280**	**All**	**320**
No. pts	51	85	66	151	136	112	248	272	178	450	753
Cumulative dose mg/m²											
Median	1259.8	918.9	563.3	822.6	1251.0	564.6	919.1	1183.0	564.1	918.6	886.3
Minimum	305.7	309.3	204.3	204.3	107.7	127.7	107.7	107.7	127.7	107.7	0.0*
Maximum	3755.6	6812.4	3067.9	6812.4	4807.4	5642.6	5642.6	6812.4	5642.6	6812.4	6389.5
Dose intensity per patient (mg/m²/week)											
Median	101.9	100.0	91.7	93.6	99.6	89.3	93.3	100.0	89.5	94.2	104.6
Minimum	75.7	50.5	41.7	41.7	18.4	42.6	18.4	18.4	41.7	18.4	0.0*
Maximum	109.1	115.0	102.3	115.0	109.8	100.5	109.8	115.0	102.3	115.0	117.7
Relative dose intensity per patient (%)											
Median	95.5	96.6	88.7	93.8	95.4	88.4	93.0	95.6	88.5	93.7	98.3
Minimum	71.0	48.8	41.7	41.7	18.4	45.6	18.4	18.4	41.7	18.4	0.0*
Maximum	102.2	113.0	100.6	113.0	103.4	107.7	107.7	113.0	107.7	113.0	110.6

- Adverse events

The following table summarizes the study treatment related adverse events of special interest worst grade by patient (TCCU and Non-TCCU patients).

Table 31. Study Treatment Related Adverse Events with Vinflunine

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
ANY ADVERSE EVENT	**255(93.8%)**	120(44.1%)	**165(92.7%)**	100(56.2%)	**420(93.3%)**	220(48.9%)	**676(89.8%)**	281(37.3%)
Blood and lymphatic system disorders	**21(7.7%)**	20(7.4%)	**12(6.7%)**	12(6.7%)	**33(7.3%)**	32(7.1%)	**34(4.5%)**	33(4.4%)
- **Disseminated intravascular coagulation**			**1(0.6%)**	1(0.6%)	**1(0.2%)**	1(0.2%)		
- **Febrile neutropenia**	**19(7.0%)**	19(7.0%)	**11(6.2%)**	11(6.2%)	**30(6.7%)**	30(6.7%)	**34(4.5%)**	33(4.4%)
- **Pancytopenia**	**2(0.7%)**	1(0.4%)			**2(0.4%)**	1(0.2%)		
Cardiac disorders	**9(3.3%)**	4(1.5%)	**5(2.8%)**	2(1.1%)	**14(3.1%)**	6(1.3%)	**15(2.0%)**	3(0.4%)
- **Arrhythmia supraventricular**							**1(0.1%)**	
- **Atrial fibrillation**							**1(0.1%)**	
- **Bradycardia**							**1(0.1%)**	1(0.1%)
- **Cardiac failure**							**1(0.1%)**	1(0.1%)

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Cardio-respiratory arrest	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)		
- Cardiogenic shock							1(0.1%)	1(0.1%)
- Myocardial infarction			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Myocardial ischaemia	2(0.7%)	2(0.7%)	1(0.6%)	1(0.6%)	3(0.7%)	3(0.7%)	2(0.3%)	1(0.1%)
- Palpitations	2(0.7%)				2(0.4%)		4(0.5%)	
- Sinus tachycardia	1(0.4%)	1(0.4%)	2(1.1%)		3(0.7%)	1(0.2%)	1(0.1%)	
- Supraventricular extrasystoles	1(0.4%)				1(0.2%)			
- Tachycardia	2(0.7%)		1(0.6%)		3(0.7%)		4(0.5%)	
Ear and labyrinth disorders	9(3.3%)	1(0.4%)	5(2.8%)	1(0.6%)	14(3.1%)	2(0.4%)	31(4.1%)	2(0.3%)
- Deafness							1(0.1%)	
- Ear pain	4(1.5%)		2(1.1%)		6(1.3%)		12(1.6%)	1(0.1%)
- Tinnitus	3(1.1%)		1(0.6%)		4(0.9%)		6(0.8%)	
- Vertigo	2(0.7%)	1(0.4%)	1(0.6%)	1(0.6%)	3(0.7%)	2(0.4%)	14(1.9%)	1(0.1%)
- Vertigo positional			1(0.6%)		1(0.2%)			
Endocrine disorders							3(0.4%)	3(0.4%)
- Inappropriate antidiuretic hormone secretion							3(0.4%)	3(0.4%)
Eye disorders	4(1.5%)		1(0.6%)	1(0.6%)	5(1.1%)	1(0.2%)	28(3.7%)	1(0.1%)
- Blindness							1(0.1%)	
- Conjunctivitis							2(0.3%)	
- Diplopia							1(0.1%)	
- Dry eye	1(0.4%)				1(0.2%)			
- Eye pain							1(0.1%)	
- Eyelid ptosis							1(0.1%)	
- Eyelids pruritus							1(0.1%)	
- Keratoconjunctivitis sicca							1(0.1%)	
- Lacrimation increased							4(0.5%)	
- Ocular discomfort							1(0.1%)	
- Photopsia							1(0.1%)	
- Retinal vein thrombosis			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Vision blurred	1(0.4%)				1(0.2%)		16(2.1%)	1(0.1%)
- Visual acuity reduced	1(0.4%)				1(0.2%)			
- Visual disturbance							1(0.1%)	
- Vitreous floaters	1(0.4%)				1(0.2%)			
Gastrointestinal disorders	219(80.5%)	56(20.6%)	144(80.9%)	55(30.9%)	363(80.7%)	111(24.7%)	591(78.5%)	146(19.4%)
- Abdominal discomfort	2(0.7%)		1(0.6%)	1(0.6%)	3(0.7%)	1(0.2%)	2(0.3%)	
- Abdominal distension	3(1.1%)		2(1.1%)		5(1.1%)		4(0.5%)	1(0.1%)
- Abdominal pain	47(17.3%)	7(2.6%)	29(16.3%)	11(6.2%)	76(16.9%)	18(4.0%)	200(26.6%)	44(5.8%)
- Abdominal pain lower	2(0.7%)		1(0.6%)		3(0.7%)		1(0.1%)	
- Abdominal pain upper	16(5.9%)	2(0.7%)	2(1.1%)	1(0.6%)	18(4.0%)	3(0.7%)	48(6.4%)	3(0.4%)
- Abdominal tenderness							2(0.3%)	
- Anal discomfort							1(0.1%)	
- Anal fistula							1(0.1%)	1(0.1%)
- Anal haemorrhage			1(0.6%)		1(0.2%)			
- Aptyalism							1(0.1%)	
- Cheilitis							1(0.1%)	
- Colonic pseudo-obstruction			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Constipation	146(53.7%)	36(13.2%)	101(56.7%)	33(18.5%)	247(54.9%)	69(15.3%)	405(53.8%)	75(10.0%)
- Diarrhoea	32(11.8%)	1(0.4%)	26(14.6%)	3(1.7%)	58(12.9%)	4(0.9%)	85(11.3%)	7(0.9%)
- Dry mouth	4(1.5%)		2(1.1%)		6(1.3%)		11(1.5%)	
- Dyspepsia	17(6.3%)		8(4.5%)	1(0.6%)	25(5.6%)	1(0.2%)	32(4.2%)	1(0.1%)
- Dysphagia	4(1.5%)	1(0.4%)	5(2.8%)	1(0.6%)	9(2.0%)	2(0.4%)	13(1.7%)	4(0.5%)
- Epigastric discomfort			1(0.6%)		1(0.2%)		1(0.1%)	
- Eructation	2(0.7%)				2(0.4%)		1(0.1%)	
- Faecal incontinence			1(0.6%)		1(0.2%)			
- Faeces discoloured	1(0.4%)				1(0.2%)			

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Flatulence	7(2.6%)		2(1.1%)		9(2.0%)		21(2.8%)	
- Gastric ulcer haemorrhage	1(0.4%)				1(0.2%)			
- Gastritis	2(0.7%)				2(0.4%)		9(1.2%)	1(0.1%)
- Gingival bleeding			1(0.6%)		1(0.2%)			
- Gingival pain	2(0.7%)				2(0.4%)		1(0.1%)	
- Glossodynia	2(0.7%)				2(0.4%)		4(0.5%)	
- Haematemesis	1(0.4%)		1(0.6%)	1(0.6%)	2(0.4%)	1(0.2%)	1(0.1%)	
- Haemorrhoids			3(1.7%)		3(0.7%)			
- Hypoaesthesia oral							2(0.3%)	
- Ileus	3(1.1%)	2(0.7%)	8(4.5%)	8(4.5%)	11(2.4%)	10(2.2%)	14(1.9%)	10(1.3%)
- Ileus paralytic	1(0.4%)	1(0.4%)	1(0.6%)	1(0.6%)	2(0.4%)	2(0.4%)		
- Intestinal obstruction	1(0.4%)				1(0.2%)			
- Intestinal spasm							1(0.1%)	
- Lip blister							1(0.1%)	
- Lip dry			1(0.6%)		1(0.2%)			
- Lip swelling							1(0.1%)	
- Melaena	1(0.4%)		1(0.6%)	1(0.6%)	2(0.4%)	1(0.2%)		
- Mouth ulceration			1(0.6%)		1(0.2%)		1(0.1%)	
- Nausea	108(39.7%)	4(1.5%)	76(42.7%)	9(5.1%)	184(40.9%)	13(2.9%)	323(42.9%)	22(2.9%)
- Odynophagia	2(0.7%)	1(0.4%)			2(0.4%)	1(0.2%)	3(0.4%)	
- Oesophagitis	1(0.4%)	1(0.4%)	1(0.6%)		2(0.4%)	1(0.2%)	1(0.1%)	
- Oral discomfort			1(0.6%)		1(0.2%)			
- Oral mucosal disorder	1(0.4%)				1(0.2%)			
- Oral pain	6(2.2%)	1(0.4%)			6(1.3%)	1(0.2%)	10(1.3%)	2(0.3%)
- Pancreatitis	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)		
- Paraesthesia oral	2(0.7%)		1(0.6%)		3(0.7%)		3(0.4%)	
- Proctalgia	1(0.4%)				1(0.2%)			
- Retching	2(0.7%)				2(0.4%)			
- Saliva altered	1(0.4%)				1(0.2%)			
- Salivary gland disorder							1(0.1%)	
- Salivary hypersecretion							2(0.3%)	
- Small intestinal obstruction			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Stomatitis	82(30.1%)	9(3.3%)	39(21.9%)	3(1.7%)	121(26.9%)	12(2.7%)	267(35.5%)	13(1.7%)
- Subileus	1(0.4%)				1(0.2%)			
- Swollen tongue	2(0.7%)		1(0.6%)		3(0.7%)		3(0.4%)	
- Tongue blistering	1(0.4%)				1(0.2%)			
- Tongue disorder							1(0.1%)	
- Tongue ulceration							3(0.4%)	
- Toothache			1(0.6%)		1(0.2%)		1(0.1%)	
- Vomiting	67(24.6%)	7(2.6%)	56(31.5%)	6(3.4%)	123(27.3%)	13(2.9%)	233(30.9%)	22(2.9%)
General disorders and administration site conditions	201(73.9%)	43(15.8%)	124(69.7%)	37(20.8%)	325(72.2%)	80(17.8%)	511(67.9%)	108(14.3%)
- Asthenia	8(2.9%)	1(0.4%)	12(6.7%)	4(2.2%)	20(4.4%)	5(1.1%)	5(0.7%)	2(0.3%)
- Catheter site rash							1(0.1%)	
- Chest discomfort							2(0.3%)	
- Chest pain	10(3.7%)	2(0.7%)	5(2.8%)	1(0.6%)	15(3.3%)	3(0.7%)	39(5.2%)	9(1.2%)
- Chills	8(2.9%)		2(1.1%)	1(0.6%)	10(2.2%)	1(0.2%)	17(2.3%)	
- Condition aggravated	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	4(0.5%)	2(0.3%)
- Early satiety			1(0.6%)		1(0.2%)			
- Extravasation	1(0.4%)		2(1.1%)		3(0.7%)		2(0.3%)	
- Facial pain	1(0.4%)				1(0.2%)			
- Fatigue	147(54.0%)	38(14.0%)	86(48.3%)	28(15.7%)	233(51.8%)	66(14.7%)	414(55.0%)	89(11.8%)
- Inflammation			1(0.6%)		1(0.2%)			
- Influenza like illness	1(0.4%)		2(1.1%)		3(0.7%)		3(0.4%)	

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Infusion related reaction	3(1.1%)		2(1.1%)		5(1.1%)			
- Infusion site erythema			1(0.6%)		1(0.2%)		8(1.1%)	
- Infusion site pain	6(2.2%)		4(2.2%)		10(2.2%)		25(3.3%)	1(0.1%)
- Infusion site phlebitis	1(0.4%)				1(0.2%)		4(0.5%)	
- Infusion site reaction	2(0.7%)		3(1.7%)		5(1.1%)		49(6.5%)	
- Infusion site swelling							1(0.1%)	
- Injection site anaesthesia							1(0.1%)	
- Injection site erythema	1(0.4%)		5(2.8%)		6(1.3%)		3(0.4%)	
- Injection site hypersensitivity	1(0.4%)				1(0.2%)			
- Injection site irritation	6(2.2%)				6(1.3%)		1(0.1%)	
- Injection site pain	10(3.7%)		10(5.6%)		20(4.4%)		5(0.7%)	
- Injection site phlebitis	4(1.5%)		7(3.9%)		11(2.4%)		4(0.5%)	
- Injection site pruritus	1(0.4%)		2(1.1%)		3(0.7%)		1(0.1%)	
- Injection site rash	1(0.4%)		1(0.6%)		2(0.4%)			
- Injection site reaction	46(16.9%)	2(0.7%)	32(18.0%)		78(17.3%)	2(0.4%)	88(11.7%)	2(0.3%)
- Injection site swelling							1(0.1%)	
- Injection site urticaria			2(1.1%)		2(0.4%)		1(0.1%)	
- Injection site vesicles							1(0.1%)	
- Local swelling							1(0.1%)	
- Malaise	2(0.7%)				2(0.4%)		1(0.1%)	
- Mucosal inflammation							1(0.1%)	
- Non-cardiac chest pain	1(0.4%)				1(0.2%)			
- Oedema	1(0.4%)				1(0.2%)		3(0.4%)	
- Oedema peripheral	3(1.1%)		2(1.1%)		5(1.1%)		2(0.3%)	
- Pain	13(4.8%)		3(1.7%)	1(0.6%)	16(3.6%)	1(0.2%)	13(1.7%)	7(0.9%)
- Peripheral coldness	1(0.4%)				1(0.2%)		1(0.1%)	
- Pyrexia	26(9.6%)		23(12.9%)	2(1.1%)	49(10.9%)	2(0.4%)	71(9.4%)	6(0.8%)
Hepatobiliary disorders	1(0.4%)				1(0.2%)		1(0.1%)	
- Hepatic pain	1(0.4%)				1(0.2%)		1(0.1%)	
Immune system disorders	5(1.8%)		4(2.2%)	1(0.6%)	9(2.0%)	1(0.2%)	12(1.6%)	2(0.3%)
- Hypersensitivity	4(1.5%)		4(2.2%)	1(0.6%)	8(1.8%)	1(0.2%)	12(1.6%)	2(0.3%)
- Seasonal allergy	1(0.4%)				1(0.2%)			
Infections and infestations	30(11.0%)	17(6.3%)	15(8.4%)	13(7.3%)	45(10.0%)	30(6.7%)	70(9.3%)	35(4.6%)
- Abscess	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Bacteraemia	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)		
- Bronchitis	2(0.7%)				2(0.4%)		4(0.5%)	1(0.1%)
- Bronchitis acute							1(0.1%)	1(0.1%)
- Candidiasis	4(1.5%)				4(0.9%)			
- Catheter related infection			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Cellulitis							2(0.3%)	2(0.3%)
- Cystitis	1(0.4%)				1(0.2%)		1(0.1%)	
- Ear infection							1(0.1%)	
- Escherichia sepsis			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Herpes simplex							5(0.7%)	1(0.1%)
- Herpes virus infection	1(0.4%)				1(0.2%)			
- Hordeolum							1(0.1%)	
- Infection	2(0.7%)	1(0.4%)			2(0.4%)	1(0.2%)	5(0.7%)	3(0.4%)
- Influenza							1(0.1%)	

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Injection site infection							1(0.1%)	
- Laryngopharyngitis							1(0.1%)	
- Lobar pneumonia							1(0.1%)	1(0.1%)
- Lower respiratory tract infection							2(0.3%)	1(0.1%)
- Lung infection							2(0.3%)	2(0.3%)
- Nasopharyngitis	1(0.4%)				1(0.2%)		1(0.1%)	
- Neutropenic infection	8(2.9%)	8(2.9%)	9(5.1%)	9(5.1%)	17(3.8%)	17(3.8%)	8(1.1%)	8(1.1%)
- Neutropenic sepsis			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	3(0.4%)	3(0.4%)
- Oral candidiasis	2(0.7%)				2(0.4%)		4(0.5%)	
- Oral infection	1(0.4%)		1(0.6%)	1(0.6%)	2(0.4%)	1(0.2%)	2(0.3%)	1(0.1%)
- Pharyngitis							6(0.8%)	1(0.1%)
- Pneumonia	4(1.5%)	4(1.5%)	1(0.6%)	1(0.6%)	5(1.1%)	5(1.1%)	3(0.4%)	1(0.1%)
- Pyelonephritis			1(0.6%)		1(0.2%)			
- Rhinitis							1(0.1%)	
- Sepsis	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Septic shock	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	3(0.4%)	3(0.4%)
- Tonsillitis							1(0.1%)	1(0.1%)
- Tooth infection							1(0.1%)	
- Upper respiratory tract infection	2(0.7%)				2(0.4%)		4(0.5%)	
- Urinary tract infection	4(1.5%)	1(0.4%)	3(1.7%)	1(0.6%)	7(1.6%)	2(0.4%)	6(0.8%)	4(0.5%)
- Vaginal candidiasis							1(0.1%)	
- Viral infection							1(0.1%)	
- Wound infection			1(0.6%)		1(0.2%)		1(0.1%)	
Injury, poisoning and procedural complications	4(1.5%)	1(0.4%)			4(0.9%)	1(0.2%)	2(0.3%)	
- Collapse of lung							1(0.1%)	
- Contusion							1(0.1%)	
- Fall	3(1.1%)	1(0.4%)			3(0.7%)	1(0.2%)		
- Ureterostomy site discomfort	1(0.4%)				1(0.2%)			
Investigations	69(25.4%)	2(0.7%)	41(23.0%)	1(0.6%)	110(24.4%)	3(0.7%)	141(18.7%)	7(0.9%)
- Alanine aminotransferase increased	1(0.4%)		1(0.6%)		2(0.4%)		1(0.1%)	1(0.1%)
- Aspartate aminotransferase increased			1(0.6%)		1(0.2%)		1(0.1%)	
- Electrocardiogram ST segment abnormal	1(0.4%)				1(0.2%)			
- Electrocardiogram T wave abnormal							1(0.1%)	
- Gamma-glutamyltransferase increased							4(0.5%)	3(0.4%)
- Neutrophil count increased	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)		
- Troponin I increased							1(0.1%)	1(0.1%)
- Weight decreased	68(25.0%)	1(0.4%)	40(22.5%)	1(0.6%)	108(24.0%)	2(0.4%)	135(17.9%)	2(0.3%)
- Weight increased	1(0.4%)				1(0.2%)			
Metabolism and nutrition disorders	97(35.7%)	14(5.1%)	73(41.0%)	8(4.5%)	170(37.8%)	22(4.9%)	183(24.3%)	21(2.8%)
- Acidosis			1(0.6%)		1(0.2%)			
- Anorexia	91(33.5%)	8(2.9%)	64(36.0%)	4(2.2%)	155(34.4%)	12(2.7%)	176(23.4%)	14(1.9%)
- Dehydration	13(4.8%)	6(2.2%)	7(3.9%)	3(1.7%)	20(4.4%)	9(2.0%)	11(1.5%)	7(0.9%)
- Gout			1(0.6%)		1(0.2%)			
- Hyperglycaemia	1(0.4%)	1(0.4%)	2(1.1%)	2(1.1%)	3(0.7%)	3(0.7%)	2(0.3%)	2(0.3%)
- Hypoalbuminaemia	1(0.4%)				1(0.2%)			
- Hypoglycaemia	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	1(0.1%)	
- Hypomagnesaemia	1(0.4%)		1(0.6%)		2(0.4%)			
- Hypovolaemia			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
Musculoskeletal and connective tissue disorders	105(38.6%)	17(6.3%)	42(23.6%)	8(4.5%)	147(32.7%)	25(5.6%)	254(33.7%)	42(5.6%)

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Arthralgia	20(7.4%)	2(0.7%)	12(6.7%)	1(0.6%)	32(7.1%)	3(0.7%)	74(9.8%)	11(1.5%)
- Back pain	17(6.3%)	2(0.7%)	5(2.8%)		22(4.9%)	2(0.4%)	19(2.5%)	2(0.3%)
- Bone pain	10(3.7%)		1(0.6%)		11(2.4%)		19(2.5%)	6(0.8%)
- Flank pain	3(1.1%)				3(0.7%)		2(0.3%)	1(0.1%)
- Groin pain	1(0.4%)		1(0.6%)	1(0.6%)	2(0.4%)	1(0.2%)	1(0.1%)	
- Joint stiffness	1(0.4%)				1(0.2%)			
- Muscle contracture	1(0.4%)				1(0.2%)			
- Muscle spasms	6(2.2%)		2(1.1%)		8(1.8%)		6(0.8%)	
- Muscular weakness	4(1.5%)	1(0.4%)	6(3.4%)	3(1.7%)	10(2.2%)	4(0.9%)	17(2.3%)	2(0.3%)
- Musculoskeletal chest pain	4(1.5%)	1(0.4%)	1(0.6%)		5(1.1%)	1(0.2%)	1(0.1%)	
- Musculoskeletal discomfort							1(0.1%)	
- Musculoskeletal pain	7(2.6%)		2(1.1%)		9(2.0%)		4(0.5%)	1(0.1%)
- Musculoskeletal stiffness	1(0.4%)				1(0.2%)		1(0.1%)	1(0.1%)
- Myalgia	54(19.9%)	11(4.0%)	20(11.2%)	3(1.7%)	74(16.4%)	14(3.1%)	146(19.4%)	26(3.5%)
- Myositis							1(0.1%)	
- Neck pain	5(1.8%)		2(1.1%)		7(1.6%)		5(0.7%)	
- Pain in extremity	12(4.4%)		3(1.7%)		15(3.3%)		13(1.7%)	1(0.1%)
- Pain in jaw	10(3.7%)		5(2.8%)		15(3.3%)		50(6.6%)	6(0.8%)
- Polyarthritis							1(0.1%)	
- Trismus	1(0.4%)				1(0.2%)		1(0.1%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4(1.5%)	1(0.4%)	2(1.1%)		6(1.3%)	1(0.2%)	17(2.3%)	4(0.5%)
- Cancer pain	4(1.5%)	1(0.4%)	1(0.6%)		5(1.1%)	1(0.2%)	16(2.1%)	4(0.5%)
- Metastatic pain			1(0.6%)		1(0.2%)		2(0.3%)	
Nervous system disorders	77(28.3%)	10(3.7%)	41(23.0%)	7(3.9%)	118(26.2%)	17(3.8%)	210(27.9%)	17(2.3%)
- Ageusia			1(0.6%)		1(0.2%)			
- Akinaesthesia							1(0.1%)	
- Amnesia							1(0.1%)	1(0.1%)
- Aphonia							2(0.3%)	
- Areflexia							3(0.4%)	
- Burning sensation							2(0.3%)	
- Convulsion			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	2(0.3%)	2(0.3%)
- Coordination abnormal							1(0.1%)	
- Depressed level of consciousness			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Disturbance in attention							2(0.3%)	
- Dizziness	16(5.9%)	1(0.4%)	8(4.5%)	1(0.6%)	24(5.3%)	2(0.4%)	27(3.6%)	2(0.3%)
- Dysaesthesia							1(0.1%)	
- Dysgeusia	6(2.2%)		7(3.9%)		13(2.9%)		24(3.2%)	
- Dysphasia							1(0.1%)	
- Extrapyramidal disorder							2(0.3%)	1(0.1%)
- Headache	20(7.4%)	2(0.7%)	8(4.5%)	1(0.6%)	28(6.2%)	3(0.7%)	65(8.6%)	4(0.5%)
- Hyperaesthesia	1(0.4%)				1(0.2%)			
- Hypersomnia			1(0.6%)		1(0.2%)			
- Hypoaesthesia	5(1.8%)		2(1.1%)		7(1.6%)		8(1.1%)	
- Lethargy	2(0.7%)				2(0.4%)		2(0.3%)	
- Neuralgia	18(6.6%)	1(0.4%)	9(5.1%)	1(0.6%)	27(6.0%)	2(0.4%)	34(4.5%)	4(0.5%)
- Neuropathy	4(1.5%)		1(0.6%)		5(1.1%)			
- Neuropathy peripheral	4(1.5%)				4(0.9%)			
- Paraesthesia	12(4.4%)	1(0.4%)	6(3.4%)	1(0.6%)	18(4.0%)	2(0.4%)	71(9.4%)	3(0.4%)
- Parosmia							3(0.4%)	
- Peripheral motor neuropathy	2(0.7%)		1(0.6%)		3(0.7%)		3(0.4%)	1(0.1%)
- Peripheral sensory neuropathy	16(5.9%)	1(0.4%)	4(2.2%)	1(0.6%)	20(4.4%)	2(0.4%)	22(2.9%)	1(0.1%)
- Peroneal nerve palsy							1(0.1%)	

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Restless legs syndrome							1(0.1%)	
- Sinus headache							1(0.1%)	1(0.1%)
- Somnolence							1(0.1%)	
- Syncope	4(1.5%)	4(1.5%)			4(0.9%)	4(0.9%)	1(0.1%)	
- Syncope vasovagal	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)	2(0.3%)	
- Tremor	1(0.4%)		1(0.6%)		2(0.4%)			
- Trigeminal neuralgia							1(0.1%)	
Psychiatric disorders	17(6.3%)	2(0.7%)	18(10.1%)	2(1.1%)	35(7.8%)	4(0.9%)	40(5.3%)	9(1.2%)
- Agitation							1(0.1%)	1(0.1%)
- Anxiety	2(0.7%)		3(1.7%)		5(1.1%)		9(1.2%)	2(0.3%)
- Confusional state	1(0.4%)	1(0.4%)	1(0.6%)	1(0.6%)	2(0.4%)	2(0.4%)	7(0.9%)	4(0.5%)
- Depressed mood							2(0.3%)	
- Depression	2(0.7%)		2(1.1%)		4(0.9%)		1(0.1%)	
- Disorientation			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Emotional disorder							1(0.1%)	
- Insomnia	12(4.4%)	1(0.4%)	10(5.6%)		22(4.9%)	1(0.2%)	22(2.9%)	3(0.4%)
- Mood altered							1(0.1%)	
- Nervousness							1(0.1%)	
- Restlessness			1(0.6%)		1(0.2%)		2(0.3%)	
- Sleep disorder			1(0.6%)		1(0.2%)			
Renal and urinary disorders	7(2.6%)		3(1.7%)	1(0.6%)	10(2.2%)	1(0.2%)	8(1.1%)	2(0.3%)
- Dysuria	2(0.7%)				2(0.4%)		2(0.3%)	
- Haematuria	3(1.1%)		1(0.6%)		4(0.9%)		1(0.1%)	
- Haemoglobinuria							1(0.1%)	
- Micturition disorder			1(0.6%)		1(0.2%)			
- Nocturia	1(0.4%)				1(0.2%)			
- Pollakiuria	1(0.4%)				1(0.2%)		1(0.1%)	
- Renal colic	1(0.4%)				1(0.2%)			
- Renal failure			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Renal pain							1(0.1%)	1(0.1%)
- Renal tubular necrosis							1(0.1%)	1(0.1%)
- Urinary incontinence							1(0.1%)	
Reproductive system and breast disorders	3(1.1%)	1(0.4%)	4(2.2%)	1(0.6%)	7(1.6%)	2(0.4%)	3(0.4%)	
- Erectile dysfunction							1(0.1%)	
- Pelvic pain	2(0.7%)	1(0.4%)	4(2.2%)	1(0.6%)	6(1.3%)	2(0.4%)	2(0.3%)	
- Penile discharge	1(0.4%)				1(0.2%)			
- Penile pain			1(0.6%)		1(0.2%)			
Respiratory, thoracic and mediastinal disorders	23(8.5%)	3(1.1%)	21(11.8%)	6(3.4%)	44(9.8%)	9(2.0%)	52(6.9%)	17(2.3%)
- Acute respiratory distress syndrome			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	2(0.3%)	2(0.3%)
- Bronchospasm							1(0.1%)	1(0.1%)
- Cough	6(2.2%)		4(2.2%)		10(2.2%)		8(1.1%)	
- Cryptogenic organising pneumonia	1(0.4%)	1(0.4%)	1(0.6%)		2(0.4%)	1(0.2%)		
- Dry throat							1(0.1%)	
- Dysphonia	2(0.7%)				2(0.4%)		3(0.4%)	
- Dyspnoea	8(2.9%)		8(4.5%)	2(1.1%)	16(3.6%)	2(0.4%)	24(3.2%)	13(1.7%)
- Dyspnoea exertional	1(0.4%)		2(1.1%)		3(0.7%)			
- Epistaxis	2(0.7%)		3(1.7%)	1(0.6%)	5(1.1%)	1(0.2%)	7(0.9%)	
- Haemoptysis	1(0.4%)				1(0.2%)		2(0.3%)	
- Hiccups	2(0.7%)				2(0.4%)		2(0.3%)	
- Hypoxia							1(0.1%)	
- Interstitial lung disease							1(0.1%)	1(0.1%)
- Lung disorder			1(0.6%)		1(0.2%)			
- Pharyngolaryngeal pain	4(1.5%)				4(0.9%)		4(0.5%)	
- Pleural effusion							1(0.1%)	1(0.1%)
- Pneumonitis	1(0.4%)				1(0.2%)			
- Productive cough	1(0.4%)		1(0.6%)		2(0.4%)		1(0.1%)	

MedDRA class - n (%)	TCCU 320 mg/m² (N=272)		TCCU 280 mg/m² (N=178)		TCCU ALL (N=450)		Non-TCCU (N=753)	
SYSTEM ORGAN/PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Pulmonary embolism	1(0.4%)	1(0.4%)	2(1.1%)	2(1.1%)	3(0.7%)	3(0.7%)	1(0.1%)	1(0.1%)
- Pulmonary oedema	1(0.4%)	1(0.4%)			1(0.2%)	1(0.2%)		
- Respiratory disorder							1(0.1%)	
- Respiratory failure							1(0.1%)	1(0.1%)
- Rhinorrhoea							1(0.1%)	
Skin and subcutaneous tissue disorders	102(37.5%)		53(29.8%)		155(34.4%)		249(33.1%)	1(0.1%)
- Acne	1(0.4%)				1(0.2%)			
- Alopecia	88(32.4%)		41(23.0%)		129(28.7%)		220(29.2%)	
- Blister	1(0.4%)				1(0.2%)			
- Dermatitis exfoliative			1(0.6%)		1(0.2%)			
- Dry skin	3(1.1%)		1(0.6%)		4(0.9%)		5(0.7%)	
- Erythema	1(0.4%)		1(0.6%)		2(0.4%)		1(0.1%)	
- Hyperhidrosis	4(1.5%)		1(0.6%)		5(1.1%)		8(1.1%)	
- Hypotrichosis			1(0.6%)		1(0.2%)			
- Nail disorder	1(0.4%)				1(0.2%)		3(0.4%)	
- Night sweats	1(0.4%)				1(0.2%)		1(0.1%)	
- Pain of skin			1(0.6%)		1(0.2%)		2(0.3%)	
- Palmar-plantar erythrodysaesthesia syndrome			1(0.6%)		1(0.2%)		1(0.1%)	
- Pigmentation disorder			1(0.6%)		1(0.2%)		2(0.3%)	
- Pruritus	5(1.8%)		1(0.6%)		6(1.3%)		13(1.7%)	
- Pruritus generalised	1(0.4%)				1(0.2%)		1(0.1%)	
- Purpura	1(0.4%)				1(0.2%)			
- Rash	5(1.8%)		2(1.1%)		7(1.6%)		13(1.7%)	
- Rash macular							1(0.1%)	
- Rash papular							1(0.1%)	
- Skin exfoliation			1(0.6%)		1(0.2%)			
- Skin lesion	1(0.4%)				1(0.2%)		1(0.1%)	
- Skin necrosis							1(0.1%)	1(0.1%)
- Skin ulcer							1(0.1%)	
- Urticaria	4(1.5%)		2(1.1%)		6(1.3%)		4(0.5%)	
Vascular disorders	24(8.8%)	4(1.5%)	18(10.1%)	9(5.1%)	42(9.3%)	13(2.9%)	49(6.5%)	13(1.7%)
- Arteriopathic disease	1(0.4%)				1(0.2%)			
- Deep vein thrombosis	1(0.4%)	1(0.4%)	1(0.6%)	1(0.6%)	2(0.4%)	2(0.4%)		
- Flushing	2(0.7%)				2(0.4%)		8(1.1%)	
- Hot flush			1(0.6%)		1(0.2%)		8(1.1%)	
- Hypertension	7(2.6%)	2(0.7%)	8(4.5%)	6(3.4%)	15(3.3%)	8(1.8%)	19(2.5%)	10(1.3%)
- Hypertensive crisis							1(0.1%)	1(0.1%)
- Hypotension	3(1.1%)	1(0.4%)	2(1.1%)		5(1.1%)	1(0.2%)	4(0.5%)	2(0.3%)
- Hypovolaemic shock			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Ischaemia			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)		
- Lymphoedema	2(0.7%)		1(0.6%)		3(0.7%)		2(0.3%)	
- Orthostatic hypotension			1(0.6%)	1(0.6%)	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)
- Phlebitis	7(2.6%)		3(1.7%)		10(2.2%)		4(0.5%)	
- Phlebitis superficial	1(0.4%)				1(0.2%)		2(0.3%)	
- Thrombophlebitis	1(0.4%)				1(0.2%)		1(0.1%)	
- Thrombophlebitis superficial	1(0.4%)				1(0.2%)			
- Vasculitis			1(0.6%)		1(0.2%)		1(0.1%)	
- Vasospasm	1(0.4%)				1(0.2%)			

Anaemia worst grade per patient is summarized below.

Table 32: Worst grade of haemoglobin by patients and cycles

	VFL 202	VFL TCCU			Non-TCCU
Dose mg/m²	**320**	**320**	**280**	**All**	**320**
No. of patients	51	271	174	445	743
Any grade (%)	46 (90.2)	246 (90.8)	167 (96.0)	413 (92.8)	607 (81.7)
Grade 3/4 (%)	7 (13.7)	40 (14.8)	37 (21.3)	77 (17.3)	47 (6.3)

Leukopaenia worst grade per patient is summarized below.

Table 33: Worst grade of leucopenia by patient and cycles

	VFL 202	VFL TCCU			Non-TCCU
Dose mg/m²	**320**	**320**	**280**	**All**	**320**
No. of patients	51	271	174	445	743
Any grade (%)	43 (84.3)	232 (85.6)	144 (82.8)	376 (84.5)	533 (71.7)
Grade 3/4 (%)	23 (45.1)	120 (44.3)	81 (46.6)	201 (45.2)	229 (30.8)

Neutropaenia worst grade per patient is summarized below.

Table 34: Worst grade of neutropenia by patients and cycles

	VFL 202	VFL TCCU			Non-TCCU
Dose mg/m²	**320**	**320**	**280**	**All**	**320**
No. of patients	51	271	174	445	743
Any grade (%)	42 (82.4)	222 (81.9)	132 (75.9)	354 (79.6)	528 (71.1)
Grade 3/4 (%)	34 (66.7)	155 (57.2)	88 (50.6)	243 (54.6)	354 (47.6)

Thrombocytopaenia worst grade per patient is summarized below.

Table 35: Worst grade of platelets by patients and cycles

	VFL 202	VFL TCCU			Non-TCCU
Dose mg/m²	**320**	**320**	**280**	**All**	**320**
No. of patients	51	271	174	445	743
Any grade (%)	22 (43.1)	133 (49.1)	105 (60.3)	238 (53.5)	249 (33.5)
Grade 3/4 (%)	3 (5.9)	10 (3.7)	12 (6.9)	22 (4.9)	20 (2.7)

- Serious adverse event/deaths/other significant events

The incidence of SAE was 61.7% in the vinflunine + BSC arm and 47.0% in the BSC arm.

Table 36. Serious adverse events with Vinflunine (TCCU and Non-TCCU patients)

	VFL 202	CA 001			VFL302			VFL TCCU			Non-TCCU
Dose (mg/m²)	**320**	**320**	**280**	**All**	**320**	**280**	**All**	**320**	**280**	**All**	**320**
Total number of patients	51	85	66	151	136	112	248	272	178	450	753
Total number of patients with at least one SAE	25 (49.0)	34 (40.0)	43 (65.2)	77 (51.0)	78 (57.4)	75 (67.0)	153 (61.7)	137 (50.4)	118 (66.3)	255 (56.7)	330 (43.8)
Total number of patients with at least one study treatment related SAE	18 (35.3)	24 (28.2)	31(47.0)	55 (36.4)	39 (28.7)	37 (33.0)	76 (30.6)	81 (29.8)	68 (38.2)	149 (33.1)	188 (25.0)

Table 37. Study treatment related serious adverse events (TCCU and Non-TCCU patients)

MedDRA class – n (%) SYSTEM ORGAN / PREFERRED TERM	TCCU All 450	Non-TCCU 753
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**59(13.1%)**	**73(9.7%)**
- Anaemia	18(4.0%)	14(1.9%)
- Disseminated intravascular coagulation	1(0.2%)	-
- Febrile neutropenia	24(5.3%)	17(2.3%)
- Granulocytopenia	1(0.2%)	-
- Leukopenia	7(1.6%)	6(0.8%)
- Lymphopenia	1(0.2%)	-
- Neutropenia	23(5.1%)	47(6.2%)
- Pancytopenia	2(0.4%)	1(0.1%)
- Thrombocytopenia	3(0.7%)	5(0.7%)
CARDIAC DISORDERS	**4(0.9%)**	**7(0.9%)**
- Atrial fibrillation	-	1(0.1%)
- Cardio-respiratory arrest	1(0.2%)	-
- Cyanosis	-	1(0.1%)
- Myocardial infarction	1(0.2%)	2(0.3%)
- Myocardial ischaemia	1(0.2%)	1(0.1%)
- Tachycardia	1(0.2%)	4(0.5%)
EAR AND LABYRINTH DISORDERS	**2(0.4%)**	**-**
- Vertigo	2(0.4%)	-
ENDOCRINE DISORDERS	**-**	**3(0.4%)**
- Inappropriate antidiuretic hormone secretion	-	3(0.4%)
EYE DISORDERS	**2(0.4%)**	**-**
- Retinal vein thrombosis	1(0.2%)	-
- Vision blurred	1(0.2%)	-
GASTROINTESTINAL DISORDERS	**69(15.3%)**	**114(15.1%)**
- Abdominal distension	1(0.2%)	1(0.1%)
- Abdominal pain	17(3.8%)	43(5.7%)
- Abdominal pain lower	1(0.2%)	1(0.1%)
- Abdominal pain upper	2(0.4%)	2(0.3%)
- Abdominal tenderness	-	1(0.1%)
- Anal fistula	-	1(0.1%)
- Ascites	1(0.2%)	1(0.1%)
- Colonic pseudo-obstruction	1(0.2%)	-
- Constipation	35(7.8%)	65(8.6%)
- Diarrhoea	5(1.1%)	6(0.8%)
- Dyspepsia	-	2(0.3%)
- Dysphagia	3(0.7%)	3(0.4%)
- Faecaloma	1(0.2%)	-
- Gastric haemorrhage	1(0.2%)	-
- Gastric ulcer	1(0.2%)	-
- Gastritis	-	2(0.3%)
- Gastrointestinal hypomotility	1(0.2%)	-
- Hyperchlorhydria	-	1(0.1%)
- Ileus	10(2.2%)	14(1.9%)
- Ileus paralytic	1(0.2%)	1(0.1%)
- Intestinal obstruction	3(0.7%)	5(0.7%)
- Mouth ulceration	-	1(0.1%)
- Nausea	7(1.6%)	18(2.4%)
- Odynophagia	-	3(0.4%)
- Oesophagitis	1(0.2%)	-
- Oral discomfort	-	1(0.1%)
- Pancreatitis	1(0.2%)	-

MedDRA class – n (%) SYSTEM ORGAN / PREFERRED TERM	TCCU All 450	Non-TCCU 753
- Small intestinal obstruction	1(0.2%)	-
- Stomatitis	4(0.9%)	9(1.2%)
- Subileus	-	1(0.1%)
- Vomiting	13(2.9%)	34(4.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**41(9.1%)**	**66(8.8%)**
- Asthenia	5(1.1%)	10(1.3%)
- Chest discomfort	-	2(0.3%)
- Chest pain	2(0.4%)	13(1.7%)
- Chills	4(0.9%)	5(0.7%)
- Condition aggravated	6(1.3%)	9(1.2%)
- Death	-	1(0.1%)
- Extravasation	1(0.2%)	1(0.1%)
- Fatigue	14(3.1%)	8(1.1%)
- Generalised oedema	-	1(0.1%)
- Hyperthermia	1(0.2%)	-
- Inflammation	-	1(0.1%)
- Injection site erythema	-	1(0.1%)
- Injection site extravasation	-	1(0.1%)
- Injection site necrosis	-	1(0.1%)
- Injection site phlebitis	-	1(0.1%)
- Injection site reaction	1(0.2%)	5(0.7%)
- Injection site urticaria	1(0.2%)	1(0.1%)
- Malaise	-	1(0.1%)
- Mucosal inflammation	1(0.2%)	6(0.8%)
- Oedema peripheral	1(0.2%)	2(0.3%)
- Pain	-	2(0.3%)
- Pyrexia	9(2.0%)	19(2.5%)
- Sudden death	1(0.2%)	1(0.1%)
HEPATOBILIARY DISORDERS	**2(0.4%)**	**-**
- Cholestasis	1(0.2%)	-
- Hyperbilirubinaemia	1(0.2%)	-
- Jaundice	1(0.2%)	-
IMMUNE SYSTEM DISORDERS	**1(0.2%)**	**3(0.4%)**
- Hypersensitivity	1(0.2%)	3(0.4%)
INFECTIONS AND INFESTATIONS	**22(4.9%)**	**30(4.0%)**
- Abscess limb	1(0.2%)	-
- Bacteraemia	1(0.2%)	-
- Bacterial pyelonephritis	1(0.2%)	-
- Beta haemolytic streptococcal infection	-	1(0.1%)
- Breast infection	-	1(0.1%)
- Bronchitis acute	-	1(0.1%)
- Candidiasis	-	1(0.1%)
- Catheter related infection	1(0.2%)	-
- Cellulitis	-	1(0.1%)
- Clostridial infection	-	1(0.1%)
- Cystitis	1(0.2%)	
- Diverticulitis	-	1(0.1%)
- Escherichia sepsis	3(0.7%)	-
- Infection	1(0.2%)	5(0.7%)
- Injection site cellulitis	-	1(0.1%)
- Laryngitis	-	1(0.1%)
- Lobar pneumonia	-	1(0.1%)
- Lower respiratory tract infection	-	1(0.1%)
- Lung infection	-	1(0.1%)

MedDRA class – n (%) SYSTEM ORGAN / PREFERRED TERM	TCCU All 450	Non-TCCU 753
- Neutropenic infection	9(2.0%)	8(1.1%)
- Neutropenic sepsis	1(0.2%)	3(0.4%)
- Oral infection	1(0.2%)	-
- Pneumonia	4(0.9%)	1(0.1%)
- Septic shock	2(0.4%)	2(0.3%)
- Staphylococcal infection	1(0.2%)	-
- Staphylococcal sepsis	1(0.2%)	-
- Urinary tract infection	1(0.2%)	3(0.4%)
INVESTIGATIONS	**5(1.1%)**	**9(1.2%)**
- Blood bilirubin increased	-	1(0.1%)
- Blood creatinine increased	-	3(0.4%)
- Blood osmolarity decreased	-	1(0.1%)
- Blood potassium increased	-	1(0.1%)
- Blood urea increased	-	1(0.1%)
- Ecg signs of myocardial ischaemia	1(0.2%)	-
- Electrocardiogram st segment elevation	-	1(0.1%)
- Electrocardiogram t wave inversion	1(0.2%)	-
- Gamma-glutamyltransferase increased	-	1(0.1%)
- Haemoglobin decreased	2(0.4%)	-
- Neutrophil count decreased	1(0.2%)	-
- Transaminases increased	-	1(0.1%)
- Weight decreased	1(0.2%)	2(0.3%)
METABOLISM AND NUTRITION DISORDERS	**17(3.8%)**	**22(2.9%)**
- Anorexia	6(1.3%)	11(1.5%)
- Dehydration	6(1.3%)	9(1.2%)
- Hyperglycaemia	3(0.7%)	2(0.3%)
- Hypokalaemia	3(0.7%)	1(0.1%)
- Hyponatraemia	3(0.7%)	4(0.5%)
- Hypoproteinaemia	-	1(0.1%)
- Hypovolaemia	1(0.2%)	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**2(0.4%)**	**32(4.2%)**
- Arthralgia	-	10(1.3%)
- Back pain	1(0.2%)	5(0.7%)
- Bone pain	-	1(0.1%)
- Myalgia	1(0.2%)	24(3.2%)
- Neck pain	-	1(0.1%)
- Pain in jaw	-	7(0.9%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**1(0.2%)**	**3(0.4%)**
- Cancer pain	1(0.2%)	1(0.1%)
- Metastases to central nervous system	-	1(0.1%)
- Neoplasm malignant	-	1(0.1%)
NERVOUS SYSTEM DISORDERS	**9(2.0%)**	**5(0.7%)**
- Amnesia	-	1(0.1%)
- Coma	1(0.2%)	-
- Convulsion	2(0.4%)	-
- Coordination abnormal	-	1(0.1%)
- Depressed level of consciousness	-	1(0.1%)
- Dizziness	-	2(0.3%)
- Extrapyramidal disorder	-	1(0.1%)
- Formication	-	1(0.1%)
- Headache	3(0.7%)	1(0.1%)
- Hypoaesthesia	1(0.2%)	-
- Lethargy	-	1(0.1%)
- Neuralgia	2(0.4%)	1(0.1%)

MedDRA class – n (%) SYSTEM ORGAN / PREFERRED TERM	TCCU All 450	Non-TCCU 753
- Paraesthesia	1(0.2%)	1(0.1%)
- Peripheral sensorimotor neuropathy	1(0.2%)	-
- Syncope	1(0.2%)	-
- Tremor	-	1(0.1%)
PSYCHIATRIC DISORDERS	**2(0.4%)**	**6(0.8%)**
- Agitation	-	1(0.1%)
- Anxiety	-	1(0.1%)
- Confusional state	2(0.4%)	4(0.5%)
- Insomnia	-	1(0.1%)
RENAL AND URINARY DISORDERS	**3(0.7%)**	**1(0.1%)**
- Haematuria	1(0.2%)	-
- Renal colic	1(0.2%)	-
- Renal failure	1(0.2%)	-
- Renal pain	-	1(0.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1(0.2%)**	**-**
- Pelvic pain	1(0.2%)	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**6(1.3%)**	**19(2.5%)**
- Acute respiratory distress syndrome	-	1(0.1%)
- Atelectasis	-	1(0.1%)
- Bronchospasm	-	1(0.1%)
- Cough	1(0.2%)	2(0.3%)
- Cryptogenic organising pneumonia	2(0.4%)	-
- Dyspnoea	1(0.2%)	13(1.7%)
- Haemoptysis	-	1(0.1%)
- Interstitial lung disease	-	1(0.1%)
- Orthopnoea	-	1(0.1%)
- Pharyngolaryngeal pain	-	1(0.1%)
- Pleural effusion	-	2(0.3%)
- Pleuritic pain	-	1(0.1%)
- Productive cough	-	2(0.3%)
- Pulmonary embolism	2(0.4%)	-
- Pulmonary oedema	1(0.2%)	1(0.1%)
- Respiratory failure	-	1(0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1(0.2%)**	**1(0.1%)**
- Hyperhidrosis	1(0.2%)	-
- Rash erythematous	-	1(0.1%)
SURGICAL AND MEDICAL PROCEDURES	**-**	**1(0.1%)**
- Catheter placement	-	1(0.1%)
VASCULAR DISORDERS	**11(2.4%)**	**11(1.5%)**
- Axillary vein thrombosis	-	1(0.1%)
- Circulatory collapse	-	1(0.1%)
- Deep vein thrombosis	1(0.2%)	-
- Hot flush	1(0.2%)	-
- Hypertension	5(1.1%)	2(0.3%)
- Hypotension	2(0.4%)	1(0.1%)
- Hypovolaemic shock	1(0.2%)	1(0.1%)
- Ischaemia	1(0.2%)	-
- Orthostatic hypotension	1(0.2%)	1(0.1%)
- Pallor	1(0.2%)	1(0.1%)
- Phlebitis	-	2(0.3%)
- Phlebitis superficial	-	1(0.1%)
- Shock	-	1(0.1%)

Deaths

107 patients (8.9%) died within 30 days following the last vinflunine infusion. The rates of deaths within the 30 days were 7.0 % for TCCU patients in the 320 mg/m² group, 14.6% in the 280 mg/m² group and 8.2% in Non-TCCU patients. In all TCCU patients, the rate of death within 30 days was 10.0%. Twenty out of 45 deaths occurring within the 30 days following the last study drug administration were due to disease progression. The most frequent adverse event leading to death was pulmonary embolism (8 patients).

In the TCCU patients, 6 study drug related deaths were recorded, 4 in the 320 mg/m² group. Two were in relation to myelosuppression (pancytopenia, febrile neutropenia), one was in relation to septicaemia and one in relation to a cardio-pulmonary arrest. Two study drug related deaths in the 280 mg/m² group died due to infection associated with bone marrow depletion and one lethal myocardial infarction. When Non-TCCU patients were considered, 4 out of the 6 deaths due to study medication related to AEs that were a consequence of severe infection.

Table 38. Deaths within the 30 days, in TCCU and Non-TCCU patients

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose (mg/m²)	320	320	280	All	320	280	All	320	280	All	320
Total No. of patients	51	85	66	151	136	112	248	272	178	450	753
Total No. of deaths < 30 days	6 (11.8)	2 (2.4)	8 (12.1)	10 (6.6)	11 (8.1)	18 (16.1)	29 (11.7)	19 (7.0)	26 (14.6)	45 (10.0)	62 (8.2)
Death due to progression	2 (3.9)	1 (1.2)	4 (6.1)	5 (3.3)	5 (3.7)	8 (7.1)	13++ (5.2)	8 (2.9)	12 (6.7)	20 (4.4)	39 (5.2)
Death due to other reason than progression ***	4 (7.8)	1 (1.2)	4 (6.1)	5 (3.3)	6 (4.4)	10 * (8.9)	16 (6.5)	11 (4.0)	14 (7.9)	25 (5.6)	23** (3.1)
• Death due to study treatment related adverse events	2 (3.9)	1 ¯ (1.2)	2 (3.0)	3 (2.0)	1 (0.7)	0	1 (0.4)	4 (1.5)	2 (1.1)	6 (1.3)	6 (0.8)

Table 4.2.3-1; * Patient 302-050410: patient for who causality to the drug could not be answered; ** Patients 209-570108, 301-520106, 301-520231: patients for whom drug causality to the drug could not be answered; *** Include reason for death "unknown"; ++: Patient 302-780402 was not considered in the CSR 302 (died due to progression at cycle 1 day 31). ¯ In study CA001 group 320 mg/m² , patient 118-165 : in the database, this death is tabulated in 2 places with 2 different causalities (possible or not related). The related causality was considered.

Table 39. Breakdown of deaths within the 30 days in TCCU and Non-TCCU patients

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose (mg/m²)	320	320	280	All	320	280	All	320	280	All	320
Total No. of deaths < 30 days	6	2	8	10	11	18	29	19	26	45	62
Death due to progression	2 (33.3)	1 (50.0)	4 (50.0)	5 (50.0)	5 (45.5)	8 (44.4)	13 ** (44.8)	8 (42.1)	12 (46.1)	20 (44.4)	39 (62.9)
Death due to other reason than progression***	4 (66.7)	1 (50.0)	4 (50.0)	5 (50.0)	6 (54.6)	10* (55.6)	16 (55.2)	11 (57.9)	14 (53.9)	25 (55.6)	23 ** (77.1)
• Death due to study treatment related adverse event	2 (33.3)	1 ¯ (50.0)	2 (25.0)	3 (30.0)	1 (9.1)	0	1 (3.4)	4 (21.0)	2 (7.7)	6 (13.3)	6 (9.7)

Table 4.2.3-1; * Patient 302-050410: patient for who drug causality to the drug could not be answered; ** Patients 209-570108, 301-520106, 301-520231: patients for whom drug causality to the drug could not be answered; *** Include reason for death "unknown"; **: Patient 302-780402 was not considered in the CSR 302 (died due to progression at cycle 1 day 31). ¯ In study CA001 group 320 mg/m² patients 118-165. In the database, this death is tabulated in 2 places with 2 different causalities (possible or not related). The related causality was considered.

Table 40. Summary description of study drug-related adverse events leading to death in TCCU and Non TCCU patients

Study number	Patient number	Most probable cause of death	Time of death
TCCU			
VFL 202 320 mg/m² CSR L00070 IN 202 see file	130102	Septicaemia	Cycle 5 Day 11
	130601	Febrile neutropenia	Cycle 5 Day 9
CA 001 280 mg/m² CSR CA183001 see file	13-124	Infection with grade 3 – 4 neutropenia	Cycle 1 Day 8
	36-135	Myocardial infarction	Cycle 4 Day 11
CA 001 320 mg/m² CSR CA183001 see file	118-165*	Cardio Pulmonary arrest	Cycle 4 Day 14
VFL 302 320 mg/m² CSR L00070 IN 302 see file	520503	Pancytopenia	Cycle 3 Day 13
Non-TCCU			
VFL 207 CSR L00070 IN 207 see file	130205	Dehydration	Cycle 2 Day 11
VFL 208 CSR L00070 IN 208 see file	520211	Hypovolemic shock (septic)	Cycle 1 Day 17
VFL 210 CSR L00070 IN 210 see file	050207	Acute respiratory distress syndrome	Cycle 1 Day 21
VFL 211 CSR L00070 IN 211 see file	080102	Septic shock	Cycle 1 Day 13
VFL 301 CSR L00070 IN 301 see file	090104	Neutropenic infection	Cycle 1 Day 14
	570106	Neutropenic sepsis	Cycle 1 Day 10

* In study CA001 group 320 mg/m² , patient 118-165 : in the database, this death is tabulated in 2 places with 2 different causalities (possible or not related). The related causality was considered.

Table 41. Summary description of deaths within 30 days after the last administration for reasons others than progression or due to related AEs (TCCU patients)

Study number	Patient number	Most Probable cause of death	Time of death
VFL 202 320 mg/m² CSR L00070 IN 202 see file	011004	Pneumonitis	Cycle 2 Day 28
	051206	Suspected pulmonary embolism	Cycle 1 Day 9
CA 001 280 mg/m² CSR CA183001 see file	73-157	Unknown	Cycle 4 Day 29
	89-144	Pulmonary embolism	Cycle 9 Day 9
VFL 302 320 mg/m² CSR L00070 IN 302 see file	040243	Hematemesis	Cycle 1 Day 21
	520113	Bleeding from upper gastrointestinal tract	Cycle 5 Day 9
	520343	Gastrointestinal bleeding	Cycle 2 Day 6
	550302	Unknown	Cycle 2 Day 18
	550745	Cardiac pulmonary failure	Cycle 2 Day 7
VFL 302 280 mg/m² CSR L00070 IN 302 see file	020101	Deterioration of general condition	Cycle 2 Day 9
	020105	Sepsis	Cycle 2 Day 25
	030119	Renal failure	Cycle 1 Day 14
	030120	Pulmonary edema	Cycle 1 Day 9
	050410	Unknown	Cycle 1 Day 8
	110107	Intestinal subocclusion	Cycle 7 Day 21
	550249	Coma	Cycle 3 Day 18
	550643	Acute cardiac pulmonary failure	Cycle 2 Day 13
	780103	Sudden death - Unknown	Cycle 1 Day 23
	780401	Depression	Cycle 1 Day 11

Table 42. Summary description of deaths within 30 days after the last administration for reasons others than progression or due to related AEs (Non-TCCU patients)

Study number	Patient number	Most probable cause of death	Time of death
VFL 201 CSR L00070.IN.201 see file	130903	Pulmonary embolism	Cycle 1 Day 17
VFL 203 CSR L00070.IN.203 see file	130604	Pulmonary embolism	Cycle 1 Day 8
	551003	Lung artery embolism	Cycle 8 Day 25
VFL 204 CSR L00070.IN.204 see file	600602	Cerebro-vascular accident	Cycle 2 Day 10
VFL 208 CSR L00070.IN.208 see file	130102	Pulmonary embolism	Cycle 6 Day 17

Study number	Patient number	Most probable cause of death	Time of death
VFL 209 CSR L00070.IN.209 see file	570108	Unknown	Cycle 2 Day 20
VFL 301 CSR L00070.IN.301 see file	050102	Hematemesis	Cycle 1 Day 11
	050901	Budd Chiari syndrome	Cycle 3 Day 30
	051203	Pulmonary embolism	Cycle 2 Day 15
	060402	Completed Suicide	Cycle 1 Day 9
	270104	Pulmonary embolism	Cycle 3 Day 31
	520106	Sudden death (unknown)	Cycle 1 Day 7
	520231	Pulmonary oedema	Cycle 1 Day 14
	520364	Acute pulmonary oedema	Cycle 1 Day 1
	520510	Pulmonary embolism	Cycle 1 Day 7
	600202	Pulmonary embolism	Cycle 1 Day 25
	760302	Myocardial infarction	Cycle 3 Day 11

- Laboratory findings

Hematological toxicity

Neutropenia is a frequent adverse reaction of vinflunine. Adequate monitoring of complete blood counts should be conducted to verify the ANC value before each vinflunine infusion. The recommended dose should be reduced in patients with Grade>3 haematological toxicity (see section 4.2 of the SPC). Vinflunine should not be administered when the ANC < 1,000/mm^3 and/or platelets < 100,000/mm^3.

Haemoglobin.
Anaemia was commonly observed in 90.8%, 96.0% and 81.7% of the TCCU (320 mg/m²), TCCU (280 mg/m²) and Non-TCCU patients, respectively. In the BSC arm of the Phase III trial (VFL 302), 2/3 of patients (61.3%) also experienced anaemia.

During the treatment period, severe anaemia (grade 3, haemoglobin ≥ 6.5 g/dl < 8.0 g/dl; or grade 4, haemoglobin < 6.5g/dl) was recorded in 14.8 % of TCCU (320 mg/m²) patients and in 21.3 % TCCU (280 mg/m²) patients. Grade 4 anaemia was rare, occurring in only 5 patients (1.8%) in the TCCU (320 mg/m²), and 7 cases (4.0%) in the TCCU patients treated at 280 mg/m². Grade 3/4 anaemia occurred in 5.9% of cycles in the TCCU patients and in 1.9% of the cycles in Non-TCCU patients.

Seven percent (6.8%) of the patients had no anaemia at baseline, but experienced grade 3/4 anaemia as the worst grade during treatment. Forty seven percent (568/1203) of patients treated with VFL presented with anaemia at baseline. Among patients presenting with grade 1/2 at baseline anaemia worsened to reach grade 3/4 events in 27.2% of patients during treatment.

Leucocytes
A total of 120 (44.3%) of the TCCU patients in the 320 mg/m² group and 81 (46.6%) of the 280 mg/m² group experienced grade 3/4 leucopenia during vinflunine treatment. In Non-TCCU patients, the incidence of grade 3/4 leucopenia is lower (30.8%).

At baseline, TCCU patients were required to have a baseline neutrophils (ANC) value of at least 1.5 x 10^9/L in VFL 302 and CA 001 studies and of 2.0 x 10^9/L in the VFL 202 study.

Neutropenia was commonly observed in all data sets. Grades 3/4 severity was recorded in 57.2%, 50.6% and 47.6% of patients in TCCU (320 mg/m²), TCCU (280 mg/m²) and Non-TCCU patients, respectively. Grade 3/4 neutropenia induced few major clinical consequences:

- Febrile neutropenia was recorded in 7% of the TCCU patients treated at 320 mg/m² (1.8% of cycle), 6.2% of patients treated at 280 mg/m² (1.8% of cycles) and in 4.5% of Non-TCCU patients (1.3% of cycles); only one patient died due to this adverse event (Patient 202-130601).

- Infections with severe neutropenia and any grade of infection were observed in 4.7% of TCCU patients (4.0% treated at 320 mg/m² and 5.6% treated at 280 mg/m²) and in 2.5% of Non-TCCU patients.

- The rate of severe infection with severe neutropenia was very low (grade 4 life threatening sepsis (e.g. septic shock): 1.1% of TCCU patients).

- Overall 7 deaths were reported (0.5%) from infection as a complication occurring during neutropenia. Five of those 7 deaths were observed in second line treatment (Two in NSCLC patients 301-090104, 301-570106; one in ovarian cancer patient 208-520211 and two in TCCU patients 202-130102, CA001-13-124).

- Among the patients treated at the recommended dose of 320 mg/m², the median nadir of neutrophils at cycle 1was observed at 0.9 x 10^9 L (range [0 ; 2.8 x 10^9 L] at the 8.5 day ,range [7 ; 17]. These values have been obtained from the phase I study in which WBC counts were performed twice every week.

Platelets

In TCCU trials, grade 3/4 thrombocytopenia was reported in 10 patients (3.7%) among those treated at 320 mg/m² and in 12 patients (6.9%) among those treated at 280 mg/m², as compared to Non-TCCU patients (2.7%). In all studies, the threshold baseline value of platelets was 100 x 10^9/L.

Gastrointestinal disorders

Severe constipation occurred in 15.3% of treated patients. Constipation is reversible and not cumulative. Special dietary measures such as oral hydration should be taken and laxatives should be administered from day 1 to day 5 or 7 of the treatment cycle. Patients at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior heavy abdominal surgery) should be medicated with polyethylene glycol from day 1 to day 7 administered once a day in the morning before breakfast.
In case of Grade 2 constipation for more than 5 days and Grade≥ 3 of any duration, the dose of vinflunine should be adjusted (see section 4.2 of the SPC).

Therefore, the following warning was adequately reflected in the SPC: The concomitant use of opioids could enhance the risk of constipation.

In case of any Grade≥ 3 gastrointestinal toxicity (except vomiting or nausea) and of mucositis (Grade 2 for more than 5 days and Grade≥ 3 of any duration) dose adjustment is required (see section 4.2 of the SPC).

Cardiac disorders

Few QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhytmias *although* no ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increase of the proarrhytmic risk (e.g., congestive heart failure, known history of QT interval prolongation, hypokalemia) (see section 4.8 of the SPC). The concomittant use of two or more QT/QTc interval prolonging drugs is not recommended (see section 4.5 of the SPC).

Special attention is recommended when vinflunine is administered to patients with prior history of myocardial infarction/ischemia or angina pectoris (see section 4.8 of the SPC). Ischaemic cardiac

events may occur, especially in patients who have underlying cardiac disease. Thus, patients receiving Javlor should be vigilantly monitored by physicians for the occurrence of cardiac events. Caution should be exercised in patients with a history of cardiac disease and the benefit / risk assessment should be carefully evaluated regularly. Discontinuation of vinflunine should be considered in patients who develop cardiac ischaemia.

Liver function
Bilirubin. Overall, the incidence of grades 3 and 4 toxicity was low and there was no relevant difference between groups: 1.9% in TCCU (320 mg/m²) patients, 2.4% in TCCU (280 mg/m²) patients, and 0.8% in Non-TCCU patients.

Table 43. Worst grade of bilirubin by patient

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose mg/m²	**320**	**320**	**280**	**All**	**320**	**280**	**All**	**320**	**280**	**All**	**320**
No. of patients	50	84	62	146	135	106	241	269	168	437	732
Any grade (%)	3 (6.0)	6 (7.1)	11 (17.1)	17 (11.6)	11 (8.1)	16 (15.1)	27 (11.2)	20 (7.4)	27 (16.1)	47 (10.8)	67 (9.2)
Grade 3/4 (%)	2 (4.0)	1 (1.2)	1 (1.6)	2 (1.4)	2 (1.5)	3 (2.8)	5 (2.1)	5 (1.9)	4 (2.4)	9 (2.1)	6 (0.8)
Grade 4 (%)	1 (2.0)	0	0	0	0	0	0	1 (0.4)	0	1 (0.2)	0

As regards to alkaline phosphatase, the picture is very similar. 18 patients (4.1%) experienced grade 3 or 4 levels.
Grade 3 and grade 4 levels of SGOT/AST and SGPT/ALT were very infrequently observed 3 cases (0.7), whatever the data set of patients.

Renal function
In studies VFL 302 and VFL 202, the lower limit of calculated creatinine clearance (Cockroft and Gault formula) for study inclusion was 40 ml/min. In the CA 001 study, this lower limit was extended to 20 ml/min. Forty three percent of TCCU patients had a creatinine clearance below normal value (< 60 mL/min) at baseline, this is probably related both to the disease setting and to prior cisplatin exposure (68.2% of patients having received a prior CDDP containing regimen). Furthermore, 6.0% of these patients had a calculated creatinine clearance lower than 40 mL/min. there was no worsening of levels of serum creatinine on study.

Serum creatinine levels observed during treatment were higher in the TCCU population (43.0%) than in the Non-TCCU patients (14.2%). The same trend is observed when considering the grade 3/4 creatininaemia which remain very low (TCCU: 1.1%, Non-TCCU: 0.4%). The difference of rate between TCCU and Non-TCCU is probably explained by the disease setting: the upper urinary tract can be impaired by the TCCU and by prior platinum containing chemotherapy (nephrotoxic agent). A total of 5 TCCU patients (1.1%) had grade 3 levels of serum creatinine during treatment. Of note, 3 (2.8%) BSC arm patients in the TCCU study VFL 302 had also grade 3 or 4 as worst grade.). In patient presenting normal values of serum creatinine at baseline, only 20% of TCCU patients treated with VFL had a grade 1 to 4 level of serum creatinine, as compared to 36% of BSC patients.

According to the NCI CTC version 2.0, Grade 3 and 4 hyponatraemia are defined as serum sodium level between 120 mmol/L to 130 mmol/L and < 120 mmol/L respectively. The incidence is slightly higher (13.7%) in TCCU patients treated at 280 mg/m². The incidence of hyponatraemia is higher in TCCU patients (11.7%) than in Non-TCCU patients (6.8%).

- Safety in special populations

Hepatic impairment
A phase I pharmacokinetic dose adjusted study of IV vinflunine in cancer patients with liver dysfunction was carried out. Both vinflunine and DVFL PK parameters showed no significant differences between patients with liver impairment and control groups. However, the safety

evaluation in the Phase I study indicated that the dose of vinflunine needed to be adjusted to 250 mg/m² for patients with moderate impairment and 200 mg/m² for patients with severe impairment. Therefore, the recommended dose should be reduced in patients with level 2 or 3 hepatic impairment (see section 4.2 of the SPC)

Group 1: Mild chronic liver dysfunction
At the recommended dose of 320 mg/m², 6 patients were treated for a total of 15 cycles. Anaemia was seen in all patients and all cycles but no grade 3 or 4 were reported. Neutropenia grade 4 was reported in 2 patients for a total of 2 cycles and a grade 3 neutropenia was reported twice in one patient. A single episode of grade 3 fatigue was described.

Group 2: Moderate chronic liver dysfunction
At the recommended dose of 250 mg/m², 6 evaluable patients. 1 experienced neutropenia and thrombocytopenia. 5 patients experienced anaemia and leucopenia. One episode of febrile neutropenia was recorded and 2 experienced grade 3 fatigue. One patient presented grade 1 neuropathy sensory. No other grades 3 or 4 non-haematological toxicities were reported in a total of 50 cycles.

Group 3: Severe chronic liver dysfunction
At the recommended dose of 200 mg/m², the 9 patients treated for a total of 37 cycles had anaemia which was graded 3 in 2 patients. Grade 3 and 4 neutropenia were observed in 4 patients and grade 3 thrombocytopenia was seen in 2 patients. As regards non-haematological toxicities no grade 4 event was recorded. Five cases of grade 3 were observed, 2 patients experienced fatigue and 3 episodes of diarrhoea, gastric ulcer and melena were observed.

Table 44. Dose limiting toxicities at cycle 1 by group of liver impairment and by Vinflunine dose

Group	Vinflunine dose at cycle 1	Patient number	Dose limiting toxicity at cycle 1
1 - mild liver dysfunction	320 mg/m²	050301	GGT increase > 25%
		050402	GGT increase > 25% and grade 3 fatigue
2 - moderate liver dysfunction	320 mg/m²	050302	GGT increase > 25% and SGPT increase > 50%
		050101	Grade 3 constipation and hypertension, grade 4 fatigue
		050102	Bilirubin increase > 25%, GGT increase > 25%, SGOT increase > 50%, grade 3 constipation and grade 3 neutropenic infection
	250 mg/m²	050103	Bilirubin increase > 25%, Febrile Neutropenia
		050203	GGT increase > 25% and bilirubin increase > 25%
3 - severe liver dysfunction	250 mg/m²	050108	GGT increase > 25%
		050109	GGT increase > 25% and bilirubin increase > 25%
		050110	Grade 4 neutropenia and grade 3 constipation
	200 mg/m²	050111	Bilirubin increase > 25%
		050205	GGT increase > 25% and SGPT increase > 50%

Following the safety evaluation, the dose in patients with hepatic liver impairment is:

In patients with mild liver dysfunction (Prothrombin Time ≥70% and ULN < bilirubin ≤1.5 x ULN and/or 1.5 x ULN < transaminases ≤2.5 x ULN and/or ULN < GGT ≤5 ULN), the recommended dose of vinflunine is 320 mg/m² given on day 1 every 3 weeks

In patients with moderate chronic liver dysfunction (Child-Pugh grade A cirrhosis or prothrombin Time ≥60% and 1.5 x ULN < bilirubin ≤3 x ULN and transaminases > ULN and/or GGT > 5 x ULN) vinflunine recommended dose is 250 mg/m² on day 1 every 3 weeks;

In patients with severe chronic liver dysfunction (Child-Pugh grade B cirrhosis prothrombin Time ≥50 % and 1.5 x ULN < bilirubin >3 x ULN and transaminases > ULN and GGT > ULN) vinflunine recommended dose is 200 mg/m², on day 1 every 3 weeks.

Renal impairment

The interim analysis from a Phase I study regarding the vinflunine use in cancer patients with renal impairment was provided. Clcr of vinflunine decreased in patients with renal impairment. This decrease was of approximately 16% in patients with moderate renal impairment (Creatinine clearance (calculated) from 40 ml/min to 60 ml/min.) and of approximately 30% in patients with severe renal impairment (Creatinine clearance (calculated) from ≥20 ml/min to ≤40 ml/min). Therefore, the recommended dose should be reduced in patients with moderate or severe renal impairment (see section 4.2 of the SPC).

Dose recommendations in patients with renal impairment are as follows:
Moderate renal impairment (40 ml/min ≤ Clcr ≤ 60 ml/min): the recommended vinflunine dose is 280 mg/m²;
Severe renal impairment (20 ml/min ≤ Clcr < 40 ml/min): the recommended VFL dose is 250mg/m².

Elderly
A pharmacokinetic study of IV vinflunine in elderly cancer patients started in January 2005 and is still ongoing.

Paediatric population
No studies have been submitted in this specific population.

- Immunological events

No data was submitted with regards to immunological events. A justification was provided.

- Safety related to drug-drug interactions and other interactions

The risks of Drug Drug Interactions (DDI) were investigated through in vitro and in vivo studies as well as through population PK analysis.vinflunine Cltot statistics obtained in combined chemotherapy clinical trials are summarised in the table below.

Table 45. Safety Summary Related to DDDI with Vinflunine

Study code	Schedule of administration	Group	Nb of patients	VFL Cl_{tot} (L/h) (mean ± s.d.)	Test / Control ratio of geometric means of Cl_{tot}	$CI_{90\%}$ of the ratio of geometric means of Cl_{tot}
Early Phase I °	VFL Day 1 q3w	Control	79	42.3 ± 10.2	-	-
L00070 IN 105 J1 *See 2.7.6. see file*	VFL + CDDP Day 1 q3w	Cisplatin	30	40.5 ± 8.5	0.94	[0.86 – 1.02]
L00070 IN 107 J1 *See 2.7.6. see file*	VFL + CBDCA Day 1 q3w	Carboplatin	19	39.8 ± 7.8	0.94	[0.84 – 1.04]
L00070 IN 108J1 *See 2.7.6. see file*	VFL + PLDH Day 1 q3w	Pegylated Doxorubicin	40	30.8 ± 9.8	0.71	[0.65 - 0.78]
L00070 IN 109 B0 *See 2.7.6. see file*	VFL (Day 1) + CAP (b.i.d. Day 1 to Day 14) q3w	Capecitabine	14	43.6 ± 10.2*	0.99	[0.88 – 1.11]
L00070 IN 106 J1 *See 2.7.6. see file*	VFL (Day 1) + dFdC (Day 1 / Day 8) q3w	Gemcitabine	17	41.0 ± 7.90**	0.98	[0.88 – 1.09]
L00070 IN 111 B0 *See 2.7.6. see file*	VFL+DXR Day 1 q3w	Doxorubicin	6 (40 mg/m² DXR)	47.7 ± 12.0	n.c.	n.c.
			8 (50 mg/m² DXR)	35.7 ± 7.5	n.c.	n.c.

When combined with each chemotherapy agent, except pegylated doxorubicin hydrochloride (PLDH), vinflunine exhibited a constant clearance with less than 15% difference compared to the control values (single agent vinflunine). A significant effect of PLDH on vinflunine Cltot was demonstrated (>15% - 30% decrease). The impact of vinflunine on PLDH was a 2-3-fold apparent increase in drug clearance and volume of distribution. The mechanism of interaction was explored in vitro, demonstrating that vinflunine is strongly adsorbed on to PLDH vesicles.

A dose-finding and pharmacokinetic study of IV vinflunine combined with PLDH in a variety of advanced solid tumours was carried out (L00070 IN 1 08 J1). The study recommended two schedules for dose adjustments if combining vinflunine with PLDH. In schedule 1, the vinflunine recommended dose is 250 mg/m² together with PLDH 25 mg/m² both given on day 1 every 21 Days. In schedule 2, the vinflunine recommended dose is 170 mg/m² given on days 1 and 8 together with PLDH 25 mg/m² given on day 1, every 21 days.

Other studies indicate that only strong inhibitors of CYP3A4 such as Itraconazole, Ritonavir and ketoconazole are likely to inhibit the metabolism of vinflunine. Taxanes compounds (i.e.: paclitaxel and docetaxel) also inhibit metabolism of vinflunine but to a lesser degree. The effect of ketoconazole was confirmed in vivo in a specific Phase I study. Co-administration of ketoconazole (400 mg/day for 8 days) resulted in an increase of 31% in dose normalised AUCinf of vinflunine, a 31% increase in dose-normalized AUC (0-96h) of DVFL and a 49% increase in dose-normalized AUC (0-168h) of DVFL. Co-administration of ketoconazole at 400 mg per day for 8 days did not affect the dose-normalized Cmax of a 20 minute IV infusion of vinflunine but increased the dose-normalized Cmax for DVFL by 17%. The MTD of vinflunine is defined as 160 mg/m² when co-administered with 400 mg of ketoconazole.

- Discontinuation due to adverse events

The most common reasons for discontinuation were progressive disease (54.9%) in the vinflunine + BSC group and completion of the 18-week period (29.1%) and progressive disease (26.5%) in the BSC group.

13.1% of the patients discontinued the treatment after one cycle. 25.3% of the patients in the 280 mg/m² group received only one cycle versus 5.1% of the patients in the 320 mg/m² group. The main reasons for discontinuation after cycle 1 reported in the 280 mg/m² group were progression (20.0% of the patients) and related AEs (22.2% of the patients)

53 TCCU patients treated with vinflunine stopped their treatment due to treatment related adverse events. The table below lists the reasons for discontinuation and the number of patients discontinued in each treatment arm.

Table 46. Reasons for study discontinuation

	VFL 302	
	VFL + BSC	BSC
N	253	117
Under treatment at cut of	3 (1.2)	1 (0.9)
Completion of the 18w p	-	34 (29.1)
Progressive disease	139 (54.9)	31 (26.5)
Adverse Event	53 (20.9)	7 (6.0)
Patient's refusal	25 (9.9)	11 (9.4)
Death	16 (6.3)	20 (17.1)
Deviation	5 (2.0)	9 (7.7)
Lost to follow-up	0	1 (0.9)
Other	12 (4.7)	3 (2.6)
Total discontinued	250 (98.8)	116 (99.1)

- Post marketing experience

No postmarketing data has been submitted as this product is not commercially available, anywhere.

- Discussion on clinical safety

The overall patient exposure to vinflunine was considered adequate for safety assessment. In TCCU patients, the main toxicities of vinflunine were neutropenia, anaemia, constipation and asthenia/fatigue. All of these adverse events are considered class effects of the vinca alkaloids. The safety profile of vinflunine was similar for both TCCU and Non-TCCU populations, except for constipation, infection with severe neutropenia, stomatitis/mucositis and febrile neutropenia. The safety profile of vinflunine in both dosages groups (280 mg/m²/320 mg/m²) was comparable with slightly higher rates of AEs were seen in the 280 mg/m² group. The most frequent adverse event leading to death in all patients treated with vinflunine was pulmonary embolism. These deaths were judged not to be related to the study medication.

The following concerns were raised with regards to the clinical safety data submitted as part of this dossier.

1. The CHMP requested that the applicant provide a discussion on rarer adverse events. The applicant was also asked to comment on the type and incidence of adverse events other than 'common', particularly those related to the study medication. From the data submitted. The CHMP noted no new safety concerns. The data was considered to clarify the acceptable safety prolife of vinflunine in the proposed indication.

2. The applicant was asked to discuss the incidence of SAE in subjects treated with vinflunine, by commenting on the observed frequencies of SAE in the vinflunine + BSC arm, comparing the observed safety profile of vinflunine with other vinca alkaloids, in particular, cardiovascular and peripheral neuropathic AEs, including autonomic neuropathy. From the data submitted the CHMP considered that there were no new safety concerns. The data were considered to clarify the acceptable safety prolife of vinflunine in the proposed indication.

3. The CHMP requested that the applicant provide a full and detailed discussion on QTc interval prolongation, in line with current guidelines (CPMP/986/96 points to consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products).

Based on the applicant's response, in phase I studies, more than 100 ECGs were collected and carefully measured. QTc prolongation was not observed except in one subject whose change in QTc from baseline was found to be 67 msec at distance (~167 h) from the infusion of vinflunine at the time when plasma concentration of vinflunine had decreased to a low level of 3.7 ng/mL (higher plasma concentrations were not associated with QTc prolongation in this subject).In the clinical studies database, no adverse event of the type usually associated with torsade de pointes was observed. In addition to this, vinflunine belongs to the class of vinca alkaloids which is not known to be associated with QTc interval prolongation and its associated pro-arrhythmic events. However, the CHMP considered that there were 3 cases in the study CA183001 with a QT interval prolonged that had not been sufficiently justified. Five cases in the same study had a ΔQTcF between 31 and 60 msec and one subject had a ΔQTcF exceeding 60 msec. Despite these increases being lower than 500 msec, it could be considered as a safety problem to be taken into account.

The CHMP therefore agreed that an amendment to the SPC wording be made regarding the potential QT interval prolongation at sections 4.4, and 4.8 of the SPC.

The concomitant use of Javlor with others QT/QTc interval prolonging drugs should be avoided (see SPC section 4.4)

Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischemia were experienced by 0.6% of the patients and most of them had a pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and another one due to a cardiopulmonary arrest. Few QT interval prolongations have been observed after the administration of vinflunine. (see SPC section 4.8)

When consulted in this matter, the SAG-Oncology noted that the observed toxicity was considered as significant although the possible QTc effect did not raise particular concerns in the light of the overall toxicity profile and the applied indication, and overall agreed that due to the large unmet need in the applied indication, the safety profile did not raise particular concerns.

4. A potential risk of pancreatitis associated with vinorelbine use was recorded. Therefore, the Applicant was asked to discuss whether the risk of pancreatitis should be included in the SPC for Javlor. During vinflunine clinical trials, only 1 patient administered vinflunine injectable experienced pancreatitis NCI-CTC grade 3 (USBMS-C-20060024). This patient's medical history and concomitant drugs were considered to be pancreatitis risk factors. Therefore, the CHMP considered that the rationale to include pancreatitis as a potential side effect was not supported by the available evidence.

5. The CHMP considered it was hard to estimate the magnitude of the tolerability problems, given that gastrointestinal grade 3/4 adverse reactions were very prevalent. Therefore, the Applicant was asked to provide information about the duration and incidence per treatment cycle, the manageability of constipation with laxatives, as well as the incidence of hospitalizations per treatment cycle. Based on the Applicant's response, the CHMP noted that in general, gastrointestinal adverse events induced by vinflunine were manageable. Out of the 450 TCCU patients treated with VFL, 35 were hospitalized for constipation - 40 events in total. 18/40 of these events occurred in the phase III study. All 40 events of constipation resolved, with a median time to recovery of 5 days either after laxative treatments (osmotics and/or stimulants and/or enema) or without any specific treatment.

As well as dose reduction information following the advent of constipation, section 4.2 of the proposed SPC states '*In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration (see section 4.4)*'. Therefore, the CHMP concluded that overall, VFL induced constipation was non-cumulative, reversible, of relatively short duration and relative free of major clinical consequences.

When consulted in this matter, the SAG-Oncology noted that the observed toxicity was considered as significant although no particular concerns were raised in light of the overall toxicity profile and the applied indication, and overall agreed that due to the large unmet need in the applied indication, the safety profile did not raise particular concerns.

The SPC also includes the following:

The concomitant use of potent inhibitors or potent inducers of CYP3A4 with vinflunine should be avoided(see section 4.5 of the SPC).

When infused through a peripheral vein, vinflunine can induce Grade 1 (22%of the patients, 14.1% of the cycles), Grade 2 (11.0% of the patients, 6.8% of the cycles) or Grade 3 (0.8% of the patients, 0.2% of the cycles) venous irritation. All cases resolved rapidly without treatment discontinuation. Instructions for administration should be followed as described in section 6.6.

Men and women with reproductive potential must use an effective method of contraception during the treatment and up to 3 months after the last vinflunine administration (see section 4.6 of the SPC).

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised not to drive or use machines if they experience any adverse reaction with a potential impact on the ability to perform these activities (e.g. dizziness, syncope are common). (See SPC section 4.7 of the SPC)

The main toxic effect due to an overdose with vinflunine is bone marrow suppression with a risk of severe infection. There is no known antidote for vinflunine overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions should be closely monitored. Other appropriate measures should be taken, such as blood transfusions, administration of antibiotics and growth factors (see SPC section 4.9 of the SPC).

3.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 47. Summary of the risk management plan

<table>
<tr><th>Safety concern</th><th>Proposed pharmacovigilance activities</th><th>Proposed risk minimisation activities</th></tr>
<tr><td>Myelosuppression (neutropenia, febrile neutropenia, neutropenic infection, septic death)</td><td>Routine</td><td>Section 4.2 “Posology and method of administration”:

Paragraph “Dose adjustments due to toxicity”: based on the grade and on the nature of the event, dose adjustments are proposed. In addition, conditions for treatment delay and discontinuation are described.
<table>
<tr><td>Toxicity</td><td colspan="5">Dose adjustment</td></tr>
<tr><td>(NCI CTC v 2.0)</td><td colspan="3">Vinflunine initial dose of 320 mg/m²</td><td colspan="2">Vinflunine initial dose of 280 mg/m²</td></tr>
<tr><td></td><td>First event</td><td>2nd consecutive event</td><td>3rd consecutive event</td><td>First event</td><td>2nd consecutive event</td></tr>
<tr><td>Neutropenia Grade 4 (ANC< 500/mm3) > 7 days</td><td>280 mg/m²</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td></tr>
</table>
Section 4.3 “Contraindication”:

Vinflunine treatment is contra-indicated when neutrophil count < 1500/mm3 and /or platelets count < 100.000/mm3.

Section 4.8 “Undesirable effects”:

Summary “table” : events are presented in the SOCs “Infection and infestations” and “Blood and lymphatic system disorders”.

Paragraph “Blood and lymphatic system disorders”: the events are discussed.
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reactions</td><td colspan="2">Worst NCI Grade per patient (%)</td></tr>
<tr><td></td><td></td><td></td><td>All grades</td><td>Grade 3-4</td></tr>
<tr><td rowspan="2">Infections and infestations</td><td>Common</td><td>Neutropenic infection</td><td>3.8</td><td>3.8</td></tr>
<tr><td>Uncommon</td><td>Neutropenic sepsis</td><td>0.2</td><td>0.2</td></tr>
<tr><td rowspan="2">Blood and lymphatic system disorders</td><td>Very common</td><td>Neutropenia</td><td>79.6</td><td>54.6</td></tr>
<tr><td>Common</td><td>Febrile neutropenia</td><td>6.7</td><td>6.7</td></tr>
</table></td></tr>
<tr><td>Constipation / Ileus</td><td>Routine</td><td>Section 4.2 “Posology and method of administration”:

Paragraph “recommended co-medication”: it is mentioned “in order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration (see section 4.4)”.

Paragraph “Dose adjustments due to toxicity” : based on the grade and the length of the constipation, dose adjustments are proposed.
<table>
<tr><td>Toxicity</td><td colspan="4">Dose adjustment</td></tr>
<tr><td>(NCI CTC v 2.0)</td><td colspan="3">Vinflunine initial dose of 320 mg/m²</td><td colspan="2">Vinflunine initial dose of 280 mg/m²</td></tr>
<tr><td></td><td>First event</td><td>2nd consecutive event</td><td>3rd consecutive event</td><td>First event</td><td>2nd consecutive event</td></tr>
<tr><td>Mucositis or Constipation Grade 2 ≥ 5 days or ≥ 3 any duration</td><td>280 mg/m²</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td></tr>
</table>
Section 4.4 “Special warning and precautions for use”:</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
Paragraph "gastrointestinal disorders": recommendations about prophylaxis for patients (including patients at high risk of constipation) are presented. The definition of "patients at high risk of constipation" is provided.

Section 4.5 "Interaction with other medicinal products and other forms of interaction":

It is mentioned that "The concomitant use of opioïds could enhance the risk of constipation"

Section 4.8 "Undesirable effects":

Summary "table" : events are presented in the SOC "Gastrointestinal disorders".

Paragraph "Gastrointestinal disorders": the events are discussed.
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reactions</td><td colspan="2">Worst NCI Grade per patient (%)</td></tr>
<tr><td></td><td></td><td></td><td>All grades</td><td>Grade 3-4</td></tr>
<tr><td>Gastrointestinal disorders</td><td>Very common</td><td>Constipation</td><td>54.9</td><td>15.3</td></tr>
<tr><td></td><td>Common</td><td>Ileus</td><td>2.6</td><td>2.2</td></tr>
</table>
</td>
</tr>
<tr>
<td>Neurotoxicity

(peripheral sensory neuropathy, peripheral motor neuropathy, headache, dizziness, dysgueusia)</td>
<td>Routine</td>
<td>
Section 4.2 "Posology and method of administration":

Paragraph "Dose adjustments due to toxicity": based on the grade of the event, dose adjustments are proposed.
<table>
<tr><td>Toxicity</td><td colspan="5">Dose adjustment</td></tr>
<tr><td>(NCI CTC v 2.0)</td><td colspan="3">Vinflunine initial dose of 320 mg/m²</td><td colspan="2">Vinflunine initial dose of 280 mg/m²</td></tr>
<tr><td></td><td>First event</td><td>2nd consecutive event</td><td>3rd consecutive event</td><td>First event</td><td>2nd consecutive event</td></tr>
<tr><td>Any other toxicity grade ≥ 3 (except grade grade 3 vomiting or nausea)</td><td>280 mg/m²</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td><td>250 mg/m²</td><td>Definitive treatment discontinuation</td></tr>
</table>
Section 4.8 "Undesirable effects":

Summary "table" : events are presented in the SOCs "Nervous system disorders".

Paragraph "Nervous system disorders": the events are discussed as follows "Sensory peripheral neuropathy is a class effect of the vinca alkaloids. Grade 3 was experienced in 0.2% patients. All resolved during the study."
<table>
<tr><td>System Organ Class</td><td>Frequency</td><td>Adverse Reactions</td><td colspan="2">Worst NCI Grade per patient (%)</td></tr>
<tr><td></td><td></td><td></td><td>All grades</td><td>Grade 3-4</td></tr>
<tr><td>Nervous system disorders</td><td>Common</td><td>Headache</td><td>6.2</td><td>0.7</td></tr>
<tr><td></td><td></td><td>Paraesthesia</td><td>4.0</td><td>0.4</td></tr>
<tr><td></td><td></td><td>Dizziness</td><td>5.3</td><td>0.4</td></tr>
<tr><td></td><td></td><td>Neuralgia</td><td>6.0</td><td>0.4</td></tr>
<tr><td></td><td></td><td>Peripheral sensory neuropathy</td><td>4.4</td><td>0.4</td></tr>
</table>
</td>
</tr>
<tr>
<td>Ischaemic cardiac events (myocardial infarction / ischaemia, angina</td>
<td>Reinforced (routine + Annual cumulative summary and analysis of cardiac</td>
<td>
Section 4.4 "Special warning and precautions for use",

Paragraph "Cardiac disorders": "Few QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhytmias although no
</td>
</tr>
</table>

<table>
<tr>
<td>pectoris)</td>
<td>events for clinical and post-marketing survey)</td>
<td>ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increase of the proarrhytmic risk (e.g., congestive heart failure, known history of QT interval prolongation, hypokalemia) (see section 4.8). The concomittant use of two or more QT/QTc interval prolonging substances is not recommended (see section 4.5).

Special attention is recommended when vinflunine is administered to patients with prior history of myocardial infarction/ischemia or angina pectoris (see section 4.8). Ischaemic cardiac events may occur, especially in patients who have underlying cardiac disease. Thus, patients receiving Javlor should be vigilantly monitored by physicians for the occurrence of cardiac events. Caution should be exercised in patients with a history of cardiac disease and the benefit / risk assessment should be carefully evaluated regularly. Discontinuation of vinflunine should be considered in patients who develop cardiac ischaemia.”

- Section 4.5 “Interaction with others medicinal products and others forms of interaction”:
“The concomitant use of vinflunine with others QT/QTc interval prolonging drugs should be avoided (see section 4.4)”.
- Section 4.8 “Undesirable effects”:

Summary “table” : events are presented in the SOCs “Cardiac disorders”.

Paragraph “Cardiovascular disorders”: “ Cardiac effects are a known class effect of the vinca-alkaloids. Myocardial infarction or ischaemia were experienced in 0.6% of the patients. Most of them had a pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and 1 due to a cardiopulmonary arrest.”
<table>
<tr><th>System Organ Class</th><th>Frequency</th><th>Adverse Reactions</th><th colspan="2">Worst NCI Grade per patient (%)</th></tr>
<tr><td></td><td></td><td></td><td>All grades</td><td>Grade 3-4</td></tr>
<tr><td rowspan="2">Cardiac disorders</td><td rowspan="2">Uncommon</td><td>Myocardial ischaemia</td><td>0.7</td><td>0.7</td></tr>
<tr><td>Myocardial infarction</td><td>0.2</td><td>0.2</td></tr>
</table>
Since 2004 and upon AFSSaPS request, an annual cummulative summary and an analysis of cardiac events identified as potential important risk, occurring during vinflunine clinical trials have been performed. Data coming from post-marketing survey will be included in this document.</td>
</tr>
<tr>
<td>Medication errors

(incorrect routes of drug administration, mainly intrathecal)</td>
<td>Routine</td>
<td>Section 4.2 “Posology and method of administration”:

Paragraph “Method of administration”: “Javlor MUST ONLY be administered intravenously. Intrathecal administration of Javlor may be fatal.”

Section 6.6 “Special precautions for disposal and other handling and disposal”:

Paragraph “Method of administration”: it is mentioned again “For intravenous use ONLY.”

In addition, the sentences “ Intravenous use ONLY” and “IV use ONLY” are mentioned in Red respectively on the packaging and on the labels. The sentence “Fatal if given by IT route” is also mentioned in Red on the packaging, under the sentence “Intravenous use ONLY”.</td>
</tr>
</table>

Reproductive toxicity	Routine	**Section 4.3 "Contraindications":** Lactation is mentioned as contraindicated during treatment with Javlor **Section 4.6 "Pregnancy and lactation":** *Paragraph "Pregnancy":* "There is no data available on the use of vinflunine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3). On the basis of the results of animal studies and the pharmacological action of the product, there is a potential risk of embryonic and foetal abnormalities. Vinflunine should therefore not be used during pregnancy, unless it is strictly necessary. If pregnancy occurs during treatment, the patient should be informed about the risk for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy." *Paragraph "Fertility":* "Both male and female patients should take adequate contraceptive measures up to three months after the discontinuation of the therapy. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine". *Paragraph "Lactation":* It is unknown if vinflunine or its metabolites are excreted in the breast milk. Due to the possible very harmful effects on the infants, breast-feeding during treatment with vinflunine is contraindicated (see section 4.3)".
Patients with severe peripheral neuropathy	Routine	See the "proposed risk minimisation activities" presented for the important identified risk of "neurotoxicity".
Off-label use (mainly in paediatric population)	Routine	**Section 4.1 "Therapeutic indications":** "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". **Section 4.2 "Posology and method of administration":** *Paragraph "Special populations" / "Paediatric use"*: "Use in children – there is no relevant indication for use of Javlor in children".

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

3.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there is one unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. This will be addressed as part of the follow-up measure post-authorisation.

Non-clinical pharmacology and toxicology

Vinflunine distribution in rats by imaging techniques illustrated that the compound levels in lungs, kidneys, liver, salivary and endocrine glands, and gastrointestinal tract were rapidly higher than those in blood.

Preclinical data revealed moderate to severe neutropenia and mild anaemia, in all species tested, with liver toxicity in dogs and rats (characterized by dose-dependent increases in liver transaminases and hepatic necrosis/hepatocellular alterations at high doses). These toxic effects were dose-related, and fully or partially reversible following a 1-month recovery period. Vinflunine did not induce peripheral neuropathy in animals.

Vinflunine has shown to be clastogenic (induces chromosome breakage) in the *in vivo* micronucleus test in rat as well as mutagenic and clastogenic in mouse lymphoma assay (without metabolic activation).

The carcinogenic potential of vinflunine has not been studied.
In the reproduction studies, vinflunine appeared to be embryolethal and teratogenic in rabbits and teratogenic in rats.

During the pre-and post-natal development study in rat, vinflunine induced malformations of the uterus and vagina in 2 females, and adversely affected mating and/or ovule implantation and markedly lowered the number of *concepti.*

Efficacy

One phase III and two phase II trials support the use of Javlor for treatment of advanced or metastatic transitional cell carcinoma of the urothelium as second-line therapy after failure of a prior platinum-containing regimen.

In the two multi-centre open-label, single-arm phase II clinical trials a total of 202 patients were treated with vinflunine.

In the multi-centre, open-label controlled phase III clinical trial, 253 patients were randomised to treatment with vinflunine + BSC (best supportive care) and 117 patients to the BSC arm.

The median overall survival was 6.9 months (vinflunine + BSC) vs. 4.6 months (BSC), but the difference did not reach statistical significance; hazard ratio 0.88 (95% CI 0.69,1.12). However a statistically significant effect was seen on progression-free survival. Median PFS was 3.0 months (vinflunine + BSC) vs 1.5 months (BSC) (p=0.0012).

In addition a pre-specified multivariate analysis performed on the ITT population demonstrated that vinflunine had a statistically significant treatment effect (p=0.036) on overall survival when prognostic factors (PS, visceral involvement, alkaline phosphatases, haemoglobin, pelvic irradiation) were taken into consideration; hazard ratio 0.77 (95% CI 0.61, 0.98). A statistically significant difference on overall survival (p=0.040) was also seen in the eligible population (which excluded 13 patients with clinically significant protocol violations at baseline who were not eligible for treatment); hazard ratio 0.78 (95% CI 0.61, 0.99). This is considered the most relevant population for the efficacy analysis, as it most closely reflects the population intended for treatment.

Efficacy was demonstrated in both patients with and without prior cisplatin use.

In the eligible population, the subgroup analyses according to the prior cisplatin use versus BSC on overall survival (OS) showed a HR (95% CI) = [0.64 (0.40 – 1.03); p=0.0821] in the absence of prior cisplatin, and a HR (95% CI) = [0.80 (0.60 – 1.06); p=0.1263] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of OS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.53 (0.32 – 0.88); p=0.0143] and a HR (95% CI) = [0.70 (0.53 – 0.94); p=0.0174], respectively.

In the subgroup analyses of prior cisplatin use versus BSC for progression free survival (PFS), the results were: HR (95% CI) = [0.55 (0.34 – 0.89); p=0.0129] in the absence of prior cisplatin, and a HR (95% CI) = [0.64 (0.48 – 0.85); p=0.0040] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of PFS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.51(0.31 – 0.86); p=0.0111] and a HR (95% CI) = [0.63(0.48 – 0.84); p=0.0016], respectively.

Safety

The most frequent treatment-related adverse reactions reported in the two phase II and one phase III trials in patients with transitional cell carcinoma of the urothelium (450 patients treated with vinflunine) were haematological disorders, mainly neutropenia, anaemia, leucopenia and thrombocytopenia; gastrointestinal disorders, especially constipation, anorexia, nausea, stomatitis/mucositis, vomiting, abdominal pain, diarrhoea; nervous system disorders, especially peripheral sensory neuropathy; skin and subcutaneous tissue disorders, especially alopecia; musculoskeletal and connective tissue disorders, especially myalgia; general disorders, especially asthenia/fatigue, injection site reactions, pyrexia; and investigations, especially weight decrease.

Common treatment-related adverse events included neutropenic infection, viral, bacterial and fungal infections, febrile neutropenia, hypersensitivity, dehydration, insomnia, syncope, headache, dizziness, neuralgia, dysgeusia, neuropathy, ear pain, tachycardia, hypertension, vein thrombosis, hypotension, dyspnoea, cough, ileus, dysphagia, buccal disorders, dyspepsia, cutaneous reactions, pruritus, hyperhydrosis, arthralgia, back pain, pain in jaw, muscular weakness, pain in extremities, bone pain, mysculoskeletain pain, chest pain, chills, and oedemea.

Blood and lymphatic system disorders
Grade 3/4 neutropenia was observed in 54.6% of patients. Severe anaemia and thrombocytopenia were less common (respectively 17.3 and 4.9%). Febrile neutropenia defined as ANC < 1,000/mm3and fever ≥ 38.5°C of unknown origin without clinically microbiologically documented infection (NCI CTC version 2.0) was observed in 6.7% of patients. Infection with grade 3/4 neutropenia is observed in 4.2% of patients. Overall 6 patients (1.3% of the treated population) died from infection as a complication occurring during neutropenia.

Gastrointestinal disorders
Constipation is a class effect of the vinca alkaloids: 15.3% of patients experienced severe constipation during treatment with vinflunine. Grade 3/4 ileus reported in 2.7% of patients was reversible when managed by medical care. Constipation is managed by medical care (see section 4.4 of the SPC).

Nervous system disorders
Sensory peripheral neuropathy is a class effect of the vinca alkaloids. Grade 3 was experienced by 0.2% patients. All resolved during the study.

Cardiovascular disorders
Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischemia were experienced by 0.6% of the patients and most of them had a pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and another one due to a cardiopulmonary arrest.
Few QT interval prolongations have been observed after the administration of vinflunine.

Respiratory, thoracic and mediastinal disorders
Dyspnoea occurred in 3.6% of the patients but was rarely severe (Grade 3/4: 0.4%).
Bronchospam was reported in one patient treated with vinflunine for a different setting from the indication.

Eye disorders:
One case of vision blurred and visual acuity reduced have been reported.

Endocrine disorders

Three cases of suspected Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been reported in patients treated with Vinflunine for a different setting from the indication.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics (See SPC section 4.8)

Special precautions for disposal and other handling are adequately reflected in the SPC (see section 6.6).

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

The efficacy results are consistent across endpoint and a difference in survival was observed based on a number of secondary analyses, particularly in the eligible analysis and following adjustment for covariates. Secondary endpoints all favour the vinflunine arm, supporting the conclusion that the product is efficacious. No cumulative toxicities were apparent in patients with TCCU receiving vinflunine and in general, adverse events induced by vinflunine were transient and manageable.

In the eligible population, a difference in median of about 2 months survival favouring the VFL+BSC arm was observed (6.9 months vs. 4.3 months). A stratified log-rank test showed a survival difference between the 2 arms (HR 0.78 [0.61, 0.99] p=0.0403). Furthermore, a significant treatment effect of vinflunine (p=0.036) on overall survival in a multivariate Cox analysis conducted in the ITT population was seen. Vinflunine reduced the risk of death by 23% compared to BSC with a hazard ratio of 0.77 (95% CI: 0.61-0.98). Sensitivity analyses of PFS showed consistency, confirming the benefit of VFL + BSC treatment.

The pivotal study failed to achieve its primary endpoint, apparently because of the inclusion of ineligible patients who had not failed prior platinum-based chemotherapy. However, these patients with long survivals are not representative of the targeted population and might explain why the treatment effect did not reach significance in the primary analysis of the ITT population. The main toxicities of VFL were neutropenia (79.6%), anaemia (92.8%), constipation (54.9%) and asthenia/fatigue (55.3%), all these adverse events being class effects of the vinca alkaloids. The main dose limiting toxicity is neutropenia.

There is currently no standard therapy in patients with advanced urothelial carcinoma, whose disease has progressed after or during a prior platinum-containing regimen. These patients have a median survival of approximately 4 months and a poor prognosis.

The CHMP considered that the data presented support the conclusion that vinflunine has meaningful activity in this group of patients and therefore fulfils an unmet clinical need. The magnitude of the efficacy effects observed with vinflunine are comparable to those observed and considered as clinically meaningful with other anticancer drugs in different and comparable settings. This effect is supported by the positive results of vinflunine achieved on disease symptoms and all the secondary endpoints (PFS, ORR, DC). Patient exposure to vinflunine is considered adequate for safety assessment. The main toxicities of vinflunine were class effects of the vinca alkaloids. No cumulative toxicities were apparent and in general, adverse events induced by vinflunine were transient and manageable. Overall, the evidence supports a positive benefit risk balance for vinflunine in adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

A minority of CHMP members expressed a divergent view whereby the positive benefit-risk balance for Javlor was not considered to be established in the applied indication because of insufficient evidence of efficacy in the presence of significant toxicity. In particular:

- No difference in the pre-specified primary analysis of overall survival was observed for vinflunine compared to best standard of care in the intent-to-treat population, based on the single pivotal study provided.
- Where the confirmatory evidence is provided by one pivotal study only, this study has to be exceptionally compelling and special attention should be paid to internal and external validity. In the case of vinflunine, a difference in overall survival was only observed in *post hoc* exploratory analyses, excluding patients from the intent-to-treat population. However, potential biases arising from these specific exclusions, have not been adequately addressed.
- Notwithstanding the methodological flaws and potential biases associated with exploratory analyses and *post hoc* exclusion of patients, the results observed from such analyses were of very modest clinical significance in terms of overall survival or indeed any other clinically relevant endpoint, and the results lacked consistency across different analyses and subsets. Furthermore, in patients who were adequately pre-treated with cisplatin and who represent the majority of the target EU population, vinflunine showed an even lower level of activity compared to those treated with non-standard platinum compounds.
- Treatment with vinflunine was associated with significant toxicity including severe or life-threatening neutropenia, anaemia, constipation and asthenia/fatigue. Six study drug related deaths were recorded, in relation to myelosuppression, septicaemia, cardio-pulmonary arrest, infection associated with bone marrow depletion and lethal myocardial infarction.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Javlor in the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen was favourable and therefore recommended the granting of the marketing authorisation.