Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vinflunine ditartrate

Proprietary Product Name: Javlor

Sponsor: Pierre Fabre Medicament Australia Pty Ltd

April 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	7 February 2011
Active ingredient(s):	Vinflunine ditartrate
Product Name(s):	Javlor
Sponsor's Name and Address:	Pierre Fabre Medicament Australia Pty Ltd 1 Maitland Place, Baulkham Hills, NSW 2153
Dose form(s):	Concentrated Injection (see *Drug Product* below)
Strength(s):	50 mg/2 mL, 100 mg/4 mL, 250 mg/10 mL
Pack size(s):	1 vial or 10 vials (glass)
Approved Therapeutic use:	Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.
Route(s) of administration:	Intravenous (IV)
Dosage:	320 mg/m^2 every 3 weeks
ARTG Number (s)	166773, 166767 and 166772

Product Background

Pierre Fabre Medicament Australia Pty Ltd seeks to register vinflunine ditartrate concentrated injections for use in the treatment of cancer of the urothelial tract. Vinflunine is a vinca alkaloid antineoplastic drug. It binds to tubulin inhibiting polymerisation into microtubules and arresting mitosis.

Registered vinca alkaloids are vinblastine, vincristine and vinorelbine. Standard treatment for metastatic urothelial transitional cell carcinoma is a platinum-containing regimen, for example, MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)[1] or gemcitabine in combination with cisplatin. There is no standard treatment after failure of a platinum-containing regimen.

Regulatory Status

Current International Regulatory Status of Javlor (vinflunine) 25 mg/mL Concentrated Injection:

[1] http://www.cancer.gov (US National Cancer Institute).

Table 1.

Country	Approval Date	Indication	Deferrals/ Withdrawals/ Rejections
European Union (EU) Javlor is registered in all 27 EU countries plus Norway and Iceland. Via the centralised procedure: United Kingdom ((UK) rapporteur); Spain (co-rapporteur).	September 2009	Javlor is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. Efficacy and safety of vinflunine have not been studied in patients with Performance Status ≥ 2	Not applicable
Argentina	June 2010	As above.	Not applicable
Turkey	Not approved	As above.	Application received a negative opinion.

Product Information

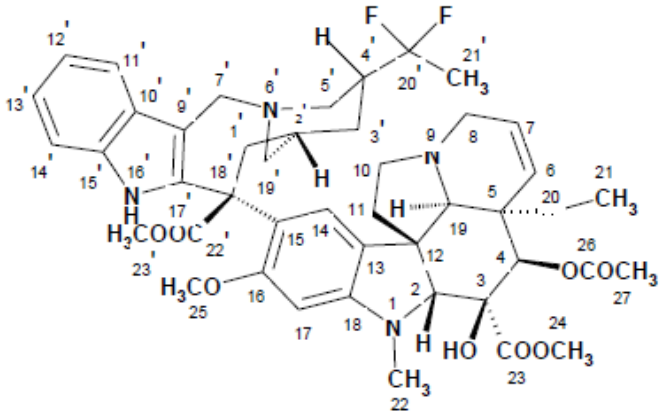
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

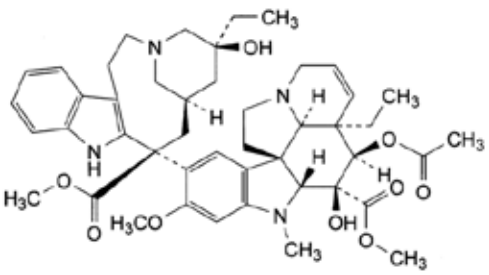
Drug Substance (active ingredient)

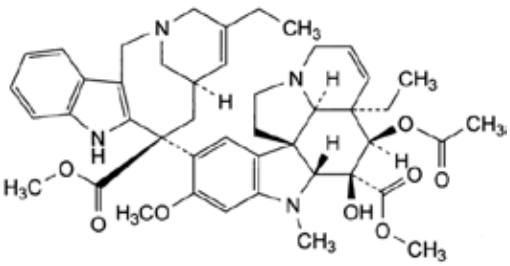
Vinflunine is a semisynthetic vinca alkaloid closely related to vinblastine, vincristine and especially vinorelbine. The drug substance is the ditartrate salt.

Figure 1. Chemical structures.



vinflunine





vinblastine vinorelbine

The drug substance is a synthetic derivative of catharanthine. The drug substance is described as “soluble” or “freely soluble” (without detailed quantification) at pH 1, 3.5 and 4.5; the base precipitates above pH 6.4. The reported pKas are 5.67 and 8.17; log P 4.2.

Drug Product

Javlor is presented as a simple aqueous solution formulated with water and nitrogen (the sponsor states that the drug substance has a strong buffering power; added buffers accelerated hydrolysis). The concentrate is sterilised by filtration. The injection concentrate is presented in clear glass vials in three fill volumes (50 mg/2 mL, 100 mg/4 mL and 250 mg/10 mL). The concentrate is diluted in either 0.9% saline or 5% glucose prior to IV infusion. The usual dose is 320 mg/m^2 as a 20 min infusion every 21 days.

Bioavailability

Javlor is only administered IV. Pharmacokinetic data are not reviewed by the Pharmaceutical Chemistry Evaluation Section of the TGA for IV injections.

Pharmaceutical Subcommittee Advice

The application was considered at the 133rd (2010/4) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommended:

RECOMMENDATION No 2140

1. There should be no objection on quality and pharmaceutic grounds to approval of the application by Pierre Fabre Medicament Australia Pty Ltd to register JAVLOR concentrated injections containing 50 mg/2 mL, 100 mg/4 mL and 250 mg/10 mL of vinflunine (as ditartrate) provided all outstanding issues are addressed to the satisfaction of the TGA.

2. The PSC endorses all the questions raised by the TGA in relation to quality and pharmaceutic issues.

3. There is no requirement for this application to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

Quality Summary and Conclusions

Chemistry and quality control issues have been satisfactorily resolved. Registration is recommended with respect to chemistry and quality control aspects.

III. Nonclinical Findings

Introduction

The overall quality of the submitted nonclinical dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (IV).

Pharmacology

Primary pharmacodynamics

The pharmacology of vinflunine ditartrate is similar to other vinca alkaloids (vinorelbine, vincristine and vinblastine), that is, cell-cycle-specific agents that block mitosis and produce metaphase arrest due to the inhibition of tubulin polymerisation, which is required for mitotic spindle formation. The interference with microtubule assembly by vinca alkaloid drugs, such

as vinflunine, leads to inhibition of mitotic spindle formation and is considered to be the major mechanism by which they exert their antitumor effects.

In vitro studies demonstrated vinflunine bound to the vinca binding site on tubulin suppressed the dynamic stability of microtubules, reduced microtubular growth rate and shortening rate and inhibited the rate of treadmilling. Overall, vinflunine had similar pharmacological properties to vinorelbine but with lower potency. Vinflunine showed some efficacy in various murine tumour-bearing models. Mice grafted with a murine bladder transitional cell carcinoma had a 60% reduction in tumour incidence when treated twice weekly with 20 mg/kg intraperitoneal (IP) vinflunine. However, vinflunine (40 mg/kg/week IP for 4 weeks) was inactive against human bladder transitional cell carcinoma xenografts in mice and was only active against some (but not all) lines of human kidney hypernephroma. Therefore, only limited data in murine tumour models support the proposed indication.

Submitted studies investigating the properties of vinflunine resistance indicated that contributing factors to resistance were an over-expression of P-glycoprotein, a down-regulation of Bcl-2[2] without alterations in either topoisomerase IIα or IIβ or multi drug resistance-associated protein (MRP) expression, or glutathione S-transferase (GST) activity or intracellular glutathione levels. Cell lines resistant to vinflunine were also resistant to other vinca alkaloids (vinorelbine, vincristine, vinblastine), colchicine (another tubulin-interacting agent) and to the topoisomerase II inhibitors, doxorubicin and etoposide. However, the vinflunine-resistant lines were still sensitive to the antimetabolites 5-fluorouracil and methotrexate, the alkylating agents cyclophosphamide and cisplatin, and the topoisomerase I inhibitor camptothecin. Further, at equivalent cytotoxic doses, resistance to vinflunine developed much later than to other vinca alkaloids.

The major human metabolite, 4-O-deacetylvinflunine, showed comparable *in vitro* cytotoxicity and microtubule inhibitory properties to vinflunine. Furthermore, a similar level of activity was observed in a tumour bearing murine model.

Secondary pharmacodynamics

In vitro, vinflunine had significant inhibitory activity at the mammalian opiate (non-specific) and m-opioid receptors with absolute inhibition constant (K_i) values of 2 and 1.1 mM, respectively (below the clinical maximal plasma concentration (C_{max}) of 15 µM [12595 ng/mL]). 4-O-deacetylvinflunine had similar inhibitory activity against these receptors (circa 3 mM). Concerns for modulation at opioid receptors in the central nervous system (CNS) are somewhat lessened by the evidence of limited blood-brain barrier crossing. As vinflunine is a substrate for P-glycoprotein, this may be the predominant mechanism for CNS exclusion. However, should vinflunine be co-administered with a P-glycoprotein inhibitor, some clinical signs of CNS activity may be seen. No significant affinity was observed against 29 other mammalian receptors at concentrations up to 10 mM. However, the tested concentrations are below the clinical C_{max} of vinflunine and 4-O-deactylvinflunine, limiting the predictive value of negative findings.

Safety pharmacology

Specialised safety pharmacology studies examined the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems. Not all of the studies were GLP-compliant but the design and conduct of the studies were considered to be (mostly) adequate to reveal any treatment-related effects.

[2] *Bcl-2* (B-cell lymphoma 2) is the founding member of the *Bcl-2* family of apoptosis regulator proteins encoded by the *BCL2* gene.

In vitro, vinflunine demonstrated dose-dependent inhibition of hERG K^+ channels with 70% inhibition at 30 mM. *In vivo*, a prolongation of QT(c)[3] interval was seen in dogs (9 mg/kg IV) and monkeys (16 mg/kg IV). These effects were seen at clinically-relevant concentrations. *In vitro*, a decrease in action potential duration in canine Purkinje fibres was seen at 100 mM vinflunine (No observable effect level (NOEL) 10 mM; exposure ratio based on C_{max} [ER_{Cmax}] 0.5), suggesting possible inhibition of calcium and/or sodium currents. Changes in other electrocardiogram (ECG) parameters (for example, an T wave amplitude increase), along with decreases in cardiac output and heart rate seen in dogs treated with 9 mg/kg IV vinflunine (ER_{Cmax} 0.4) are consistent with findings reported in animal studies with a similar compound. Adverse cardiovascular findings appear to be a class effect of vinca alkaloids and include ECG changes, variations in heart rate and blood pressure (Pai & Nahata, 2000[4]). No abnormalities in ECG parameters were seen in the 6 month monkey study at twice weekly doses up to 4 mg/kg; however, maximum blood concentrations achieved in this study were lower than those expected clinically, limiting the predictive value of findings in this study.

Dedicated studies on the respiratory system revealed respiratory depression in mice treated with 40 mg/kg IV vinflunine (estimated ER_{Cmax} 0.9). No biologically-significant respiratory effects were seen in mice at 20 mg/kg, dogs at 9 mg/kg (estimated ER_{Cmax} 0.3) or monkeys at 16 mg/kg (estimated ER_{Cmax} 0.4). As with vinorelbine, vinflunine was an inhibitor of gastric secretion in mice (50 mg/kg IV; estimated exposure based on area under the plasma concentration time curve (AUC) [ER_{AUC}] 1.6) and rats (6 mg/kg IV, ER_{AUC} 0.3) but had no effect on intestinal transit in mice and was not ulcerogenic in rats at these doses. A single dose of vinflunine had no significant effect on the renal system of rats (6 mg/kg IV, ER_{AUC} 0.3). *In vitro*, vinflunine at 100 mM inhibited platelet aggregation in rabbit blood. Similar findings have been reported for another, similar, drug. As this occurred at 5 times the clinical C_{max} it is unlikely to be clinically-relevant.

A dose-related impairment of spontaneous locomotor activity in mice was evident 10 to 20 min after IV injections of at least 12.5 mg/kg vinflunine (estimated ER_{Cmax} 0.24). Clinical signs of CNS toxicity were evident in the repeat-dose toxicity studies. These included piloerection, prostration and/or convulsions in mice at 30 mg/kg IV and rats at 3 mg/kg IV. The maximum plasma concentrations achieved at these doses were below the clinical C_{max}. Similar clinical signs were seen in repeat-dose toxicity studies with a similar compound.

Overall, the findings in safety pharmacology studies with vinflunine were broadly similar to those seen with vinorelbine and other vinca alkaloids.

Pharmacodynamic drug interactions

Drug interaction studies showed that vinflunine ditartrate (≥12.5 mg/kg IV) slightly increased the analgesic effect of morphine in mice.

[3] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

[4] Pai VB and Nahata MC (2000) Cardiotoxicity of chemotherapeutic agents. *Drug Safety* **22;** 263-302.

Pharmacokinetics

In general, exposure (based on AUC) was dose-proportional and there were no gender differences. Elimination half-lives of vinflunine after a single dose were similar in all species (4–13 h) but longer in human subjects (23 h). Serum clearance of vinflunine was similar in mice, rats, dogs and monkeys (1.4–2.3 L/h/kg), but slightly lower in human blood (0.63 L/h/kg) after a single dose. With the twice weekly dosing regimen, no significant accumulation was seen in repeat-dose toxicity studies.

The pharmacokinetic profile of the active metabolite, 4-O-deacetylvinflunine (DVFL), was also monitored. DVFL exposures were significant in mice and humans; 50-60% (on a molar AUC basis) those of vinflunine. DVFL exposures in rats and monkeys were much lower, with respective exposures 1% and 6% those of vinflunine. Vinflunine was rapidly converted to DVFL in mice (time to reach maximum serum/plasma concentration (t_{max}) 1–2 h) but much slower in other animals and humans; T_{max} 4–6 h in rats and monkeys and 14 h in humans. Elimination half-lives ($t_{1/2}$) of DVFL were in general longer than those of vinflunine and longer in humans than animals; $t_{1/2}$ 40 h in mice, 18 h in rats, 33 h in monkeys and 88 h in humans. Based on these data, DVFL is likely to contribute to the pharmacological action of vinflunine in mice and humans, but not in rats and monkeys.

Blood concentrations of vinflunine were generally higher than those in plasma (plasma:blood ratio of 0.80), indicating uptake into blood cells. Plasma protein binding of vinflunine was moderate in human sera (67% in whole blood and 79% in plasma) and mainly involved high density lipoprotein (HDL) and albumin. Binding to α_1-acid glycoprotein and to platelets was negligible. Data on the extent of protein binding in animal sera were not provided. The volume of distribution of vinflunine was high in all species and after IV administration of radioactively labelled hydrogen [^{3}H]-vinflunine to rats, rapid and widespread tissue distribution was observed. The adrenals, small intestine, spleen, Harderian gland, lung, kidney, liver, pituitary, submandibular and salivary gland had the highest level of radioactivity. Elimination was very slow from the Harderian gland, pituitary, spleen, liver, adrenals and bone marrow. There was limited penetration of the blood-brain barrier.

In all species, vinflunine was extensively metabolised through both oxidative and hydrolytic pathways. The major pathways of metabolism involved the vindoline or nor-7'velbanamine components of vinflunine. Major metabolites found in human blood (DVFL, vinflunine 6'oxide, vinflunine 3,6 ether and hydroxyvinflunine isomer 1) were found in the serum of monkeys. DVFL was also found in the blood and excreta of mice, rats and dogs. Limited additional metabolite characterisation was conducted in animal species other than monkeys, but several human metabolites were detectable in rat and dog microsome and hepatocyte incubations, suggesting they are also formed in these species. *In vitro* studies revealed a major role of cytochrome P450 (CYP) subtype 3A4 in the oxidative metabolism of vinflunine, while multiple esterases in different organs are involved in the formation of DVFL.

Drug-related material was excreted predominantly in the faeces (66-83% of the administered dose in animals and 46% in humans), with some urinary excretion detected. Unchanged vinflunine and DVFL were the dominant species in urine from mice, rats, monkeys and humans, while faecal excretion consisted mainly of metabolites, which were generally not characterised in animals. The high levels of faecal elimination for all species indicate that biliary excretion is an important route of elimination.

Overall, the pharmacokinetic profile of vinflunine was qualitatively similar across animals and humans.

Pharmacokinetic drug interactions

There was no significant inhibition of CYP2B6, 2C8, 2C9, 2C19 and 2D6 and only slight inhibition of CYP1A2 with vinflunine (50% inhibitory concentration (IC_{50}) values >30 mM; 2 times the clinical C_{max}). Significant inhibition of CYP3A4 was seen with vinflunine (IC_{50} 15 mM), consistent with the drug being a substrate of this isozyme. *In vitro,* CYP3A4 inhibitors (ketoconazole, itraconazole and ritonavir) decreased vinflunine metabolism. These *in vitro* studies also indicated docetaxel and paclitaxel could possibly inhibit vinflunine metabolism. There was no apparent induction of CYP1A2, 2B6 or 3A4 with 45 mM vinflunine.

Vinflunine, like other vinca alkaloids, is a substrate of P-glycoprotein. Over-expression of P-glycoprotein was shown to be a contributing mechanism to the resistance of cancer cells to vinflunine. Overall, inhibitors/substrates of P-glycoprotein and/or CYP3A4 are likely to alter the plasma kinetics of vinflunine and potentially increase its cytotoxic activity. The potential pharmacokinetic drug interactions with vinflunine are not dissimilar to those of a similar compound, which is also a substrate of CYP3A4 and P-glycoprotein.

An *in vitro* study indicated vinflunine was substantially adsorbed to liposomes of pegylated doxorubicin. Therefore, co-administration with pegylated doxorubicin may alter the tissue blood distribution profile and clearance of vinflunine.

Toxicology

Single dose toxicity

Single dose toxicity studies were conducted in mice, rats, dogs and monkeys and only the clinical route (IV) was used. The dog studies used ascending dose protocols and the maximum tolerated dose in this species was 9 mg/kg IV. Maximum non-lethal doses in other species were 63 mg/kg in mice, 7.5 mg/kg in rats and 16 mg/kg in monkeys and there was very little margin between non-lethal and lethal doses, suggesting a high order of toxicity in these species. Target organs for toxicity were common across the species; lymphoid tissues and bone marrow. Haematological findings included leukopaenia, neutropenia and anaemia, which developed over the post-treatment observation period (5–28 days).

Repeat-dose toxicity

Repeat-dose toxicity studies of 5 days duration were performed in mice, and up to 6 months in rats and Cynomolgus monkeys; all used the clinical route (IV). Dosing was daily in the non-pivotal mouse study, but twice weekly in rat and monkey studies. The duration of the pivotal studies, the species used (rats and monkeys), group sizes and the use of both sexes were consistent with International Conference on Harmonization (ICH) (of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines[5]. Toxicokinetic analyses were performed in all pivotal studies; exposure ratios based on animal:human AUC values are shown in Table 2. Overall, exposures achieved in animal studies were subclinical. Findings in these studies indicated the toxicity profile of vinflunine was similar to currently registered vinca alkaloid antineoplastic agents with main target organs being those with rapid cell turnover. Mortalities in toxicity studies were associated with the expected cytotoxic activity of vinflunine. Severe injection site lesions were also observed (see **Local tolerance**). No nonclinical studies have been performed to assess the toxicity of vinflunine after treatment with a platinum-containing regimen, as per the proposed clinical usage.

[5] CPMP/SWP/1042/99 Note for Guidance on Repeated Dose Toxicity and CPMP/SWP/1042/99 (revision 1) Guideline on Repeated Dose Toxicity http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm

Table 2: Relative exposure in repeat-dose toxicity studies.

Study [duration]	Species & strain [dosing interval]	Dose (mg/kg)	AUC_{0-24h} (ng·h/mL)	Exposure over[a] 3 weeks (ng·h/mL)	Exposure ratio[b]
IMT 620 [28 days]	**Rat** (SD) [twice weekly]	0.3	274	1644	0.12
		0.6	442	2652	0.19
		1.2	887	5322	0.38
		3	2092	12552	0.91
		6.4	4989	29934	2.2
IMT 677 [13 weeks]	**Rat** (SD) [twice weekly]	0.3	202	1212	0.09
		1	684	4104	0.30
		3.5	2141	12846	0.93
IMT 730 [26 weeks]	**Rat** (SD) [twice weekly]	0.3	215	1290	0.09
		0.8	653	3918	0.28
		2	1608	9648	0.70
CIT 16805 [28 days]	**Monkey** (Cynomolgus) [twice weekly]	1	711	4266	0.31
		2.2	1618	9708	0.70
		5	3618	21708	1.6
CIT 17953 [26 weeks]	**Monkey** (Cynomolgus) [twice weekly]	0.4	234	1404	0.10
		1.3	813	4878	0.35
		4	2564	15384	1.1
		10[†]	6430	38580	2.8
–	**Human**[c]	320 mg/m^2	–	13844	–

[a]Cumulative exposure over 3 weeks (AUC_{0-24h}×6); [b]Ratio of animal exposure over 3 weeks to the human exposure over 3 weeks; [c]AUC from Studies L007099 IN101 Q0 and L007099 IN102 Q0; [†]Treated for only 10-12 weeks because of mortality at this dose.

Vinflunine was hepatotoxic to rats. In both the 3 and 6 month studies, increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were evident at twice weekly doses of 3.5 mg/kg IV (ERAUC<1), with centrilobular or focal necrosis and centrilobular hypertrophy seen microscopically. As microscopic changes were seen at the low dose in the 6 month study (0.3 mg/kg twice weekly), resulting in subclinical exposures, these findings may be clinically relevant. There was no evidence of hepatotoxicity in monkeys treated for 6 months with 4 mg/kg twice weekly (ER_{AUC} 1.1). There was some evidence of reversion, although centrilobular necrosis was still evident after a 4 week treatment-free period in 4 of 5 males that had previously received 3.5 mg/kg twice weekly for 3 months. This finding is not unusual for this class of compounds.

Similar bone marrow toxicity findings were seen in rats and monkeys. Bone marrow hypocellularity was seen in rats treated twice weekly with 3.5 mg/kg IV for 6 months. Reduced myelopoiesis and erythropoiesis were seen in rats (3.5 mg/kg twice weekly) and monkeys (≥4 mg/kg twice weekly). Haematological changes subsequent to these bone marrow effects included leukopaenia, neutropenia and macrocytic regenerative anaemia (at ≥0.3 mg/kg twice weekly in rats and ≥4 mg/kg twice weekly in monkeys). Reduced levels of immunoglobulins (IgG and IgM) were seen in rats treated twice weekly with 3.5 mg/kg.

Mechanistic studies confirmed the sensitivity of erythroid and myeloid precursors to the cytotoxic nature of vinflunine. Vinflunine also inhibited the formation of megakaryocytes from human bone marrow and mononuclear cells. Bone marrow toxicity and myelosuppression have been reported for other vinca alkaloids.

Other findings include those in the thymus, probably subsequent to bone marrow toxicity (atrophy in rats, males only treated twice weekly with 3.5 mg/kg for 3 months, and lymphoid depletion in monkeys treated twice weekly with≥5 mg/kg), splenomegaly in female rats (3.5 mg/kg twice weekly for 3 months), gastrointestinal toxicity in mice (reddening of the glandular gastric wall; 30 mg/kg/day for 5 days), ocular toxicity in rats (retinal pallor and atrophied arteries; 3.5 mg/kg twice weekly for 3 months), diminished male reproductive organs in rats (3.5 mg/kg twice weekly; but with no histopathological correlates) and salivary gland hypertrophy in rats (at 6.4 mg/kg twice weekly). Haematuria was observed in rats treated twice weekly with 6.4 mg/kg vinflunine for 4 weeks, but without any correlating histopathological findings. The majority of these effects can be attributed to the pharmacological action of vinflunine and all of them have been reported with other vinca alkaloids. No novel target organs have been identified with vinflunine at doses up to those causing death or dose-limiting toxicity.

Genotoxicity

The potential genotoxicity of vinflunine was investigated in the standard battery of tests, conducted in accordance with ICH guidelines[6]. All assays were appropriately validated and were conducted under GLP conditions. Vinflunine was not mutagenic in bacterial cells but was both mutagenic and clastogenic in mammalian systems (*in vitro* in mouse lymphoma cells, with and without metabolic activation, and *in vivo* in a rat micronucleus assay). The genotoxicity findings are similar to those reported for other vinca alkaloids.

Carcinogenicity

No carcinogenicity studies were submitted, which is generally acceptable given the proposed indication. Based on the positive findings in genotoxicity assays, vinflunine ditartrate should be considered as a probable human carcinogen.

Reproductive toxicity

A standard set of GLP-compliant reproductive toxicity studies were submitted and examined both male and female fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used and dosing occurred during appropriate gestational periods. Dosing was twice weekly or every 3 days. Toxicokinetic analyses were conducted in the rabbit embryofetal toxicity study, while data for rats were extrapolated from another study (see Table 3). Exposures achieved were at or below the clinical exposure.

There were no adverse effects on counts or viability of sperm from male rats treated twice weekly for 8 weeks with vinflunine up to 3.5 mg/kg IV. At the higher twice weekly dose of 6.4 mg/kg (ER_{AUC} circa 2) used in repeat-dose toxicity studies decreased viability and motility of sperm, depressed prostate & seminal vesicle weights were seen, but with no histopathological correlates. No adverse effects on embryonic development were seen when

[6] CPMP/ICH/174/95 Note for Guidance on Genotoxicity: a Standard Battery for Genotoxicity Testing of Pharmaceuticals. http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm

treated males were mated with untreated females. There was no apparent effect on oestrus cycling or female fertility in rats treated twice weekly with 3.5 mg/kg IV vinflunine 2 weeks prior to mating, throughout mating until gestation day (GD) 7. However, when mated with treated males, there was an increase in post-implantation loss compared to untreated controls, suggesting vinflunine was embryotoxic. No effect was seen with twice weekly IV doses of 1 mg/kg (ER_{AUC} 0.32). Despite the lack of effects at doses used in these studies, impairment of fertility due to decreased sperm or ova production is expected with drugs that inhibit or interfere with normal cell production, maturation and proliferation.

Table 3: Relative exposure in reproductive toxicity studies.

Study	Species & strain [dosing interval]	Dose (mg/kg)	AUC_{0-24h} (ng·h/mL)	Exposure over 3 weeks (ng·h/mL)	Exposure ratio
Fertility[a]	**Rat** (SD) [twice weekly]	0.3	274	1644	0.12
		1	739	4434	0.32
		3.5	2441	14646	1.1
Embryofetal; Pre/postnatal[b]	**Rat** (SD) [every 3 days over GD 7-16 or GD 7-LD 21]	0.1	68	476	0.03
		0.45	280	1960	0.14
		2	1320	9240	0.67
Embryofetal[c] [98004; 98005]	**Rabbit** (NZW) [every 3 days over GD 6-18]	0.4	273	1911	0.14
		1.3	833	5831	0.42
		4	2402	16814	1.2
–	**Human**	320 mg/m^2	–	13844[†]	–

[a]Data estimated from combined male and female data in Study PK70TRH1; [b]Data estimated from female data in Study PK70TRH1; [c]Average AUC_{0-24h} from GD 6 and GD 18; [d]Cumulative exposure over 3 weeks (AUC_{0-24h}×6 for twice weekly dosing, or AUC_{0-24h}×7 for dosing every 3 days; [†]$AUC_{0-\infty}$

When administered during the period of organogenesis, vinflunine was embryo/fetotoxic and teratogenic in both rats and rabbits. An increased incidence of post-implantation loss and/or abortion was seen in rats treated with 2 mg/kg/3 days and rabbits treated with 4 mg/kg/3 days. At these same doses, an increase in fetal skeletal malformations (many misshapen or short bones) and variations (incomplete or no ossification) was seen in rats and, when treatment coincided with appropriate GDs[7], malformations of the head, brain, palate, lip, eye and ear were seen in rabbit fetuses. Embryotoxicity, fetotoxicity and teratogenicity, with similar malformations as those above, were also reported in embryofetal toxicity studies with a similar compound.

In a pre/postnatal study in rats, reduced neonatal survival (to lactation day (LD) 4) was seen in pups from dams that had been treated with 2 mg/kg/3 days IV vinflunine from GD 7 and throughout lactation, and pups from dams treated with 2 mg/kg/3 days displayed reduced body weight gain (circa 11% pre-weaning and 9% post-weaning). No adverse effects were seen on the F1[8] generation at 0.45 mg/kg/3 days. Vaginal opening did not occur in two females from dams treated with 2 mg/kg/3 days. At necropsy, segmental aplasia of the uterine

[7] According to Ecobichon (2002), in rabbit fetuses the eye develops on GD 8 and 9, which coincides with the 2nd and 1st doses administered to groups A and C respectively. Brain developmental landmarks include formation of the cerebral hemispheres on GD 11 and cerebellum on GD 15, again coinciding with treatment of Groups C (2nd dose) and A (4th dose).

[8] The F1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation).

horn was seen in a number of F1 females. This did not prevent mating or pregnancy, but implantation did not occur on the affected side of the uterus, resulting in an apparent increase in pre-implantation loss. Additional females had thin-walled or translucent uteri. Males from treated dams (2 mg/kg/3 days) had increased spontaneous locomotor activity. At necropsy, F1 males had reduced and soft testes with reduced epididymal size. The NOAEL for effects on the F1 generation was considered to be 0.45 mg/kg/
3 days (ER_{AUC} 0.14).

Local tolerance

Following IV injection to rabbits, vinflunine ditartrate (2 mg/mL in saline) produced erythema, slight oedema, sores, as well as disruption and oedema of venous drainage. In monkeys treated twice weekly with doses≥0.4 mg/kg IV, a dose-related increase in incidence and severity of perivenous collagen degradation and fibroplasia was seen microscopically at the injection site. A haematoma in subcutaneous tissue and degradation or necrosis of subcutaneous muscle were seen with twice weekly doses≥4 mg/kg IV. Following intra-arterial and paravenous injection to rabbits, vinflunine caused severe erythema, sores, macroscopic oedema of the vascular supply and epidermal ulceration. In rabbits, vinflunine ditartrate was considered to be both an ocular and a dermal irritant. A number of these local irritant effects can be attributed to the low pH of the vinflunine ditartrate solutions used (pH 3.4-3.5). No comparisons were made with currently registered vinca alkaloid formulations. Vinflunine was not apparently phototoxic in the standard 3T3 Neutral Red Uptake (NRU) phototoxicity test but, like other vinca alkaloids, it was neurotoxic in *in vitro* assays.

Toxicity of 4-O-deacetylvinflunine

The toxicity of the active metabolite, DVFL, was assessed in two single dose toxicity studies in rodents and two repeat-dose toxicity studies of 4 weeks duration in rats and monkeys. Maximum non-lethal doses in mice and rats were 25 mg/kg IV and 20 mg/kg IV, respectively, indicating high toxicity in these species. In single dose toxicity studies, clinical signs in treated animals were similar to those reported for vinflunine and included piloerection, polypnoea, dyspnoea and hypoactivity. Repeat-dose toxicity studies included vinflunine as a comparator. Findings in the rat study are difficult to interpret due to the lack of adequate toxicokinetic data and the likelihood that exposure to pharmacologically-active material would have been greater in the vinflunine group than the DVFL-treated groups. In the monkey study, findings similar to those for vinflunine were seen; leukopaenia (predominantly consisting of neutropenia), non-regenerative anaemia, bone marrow hypoplasia, shrinkage of the thymus gland and lymphoid depletion of the spleen and thymus. There was also evidence of bacteraemia in premature decedents, probably a result of severe immunosuppression. Local reactions at injection sites were similar to those for vinflunine and included scabbing, haematoma formation, sores and/or thickening. The results of the study suggested that at equimolar exposure levels the metabolite DVFL has properties similar to but more severe than the parent drug with respect to local tissue injury at the injection site, and toxicity to bone marrow resulting in anaemia and leukopaenia.

Impurities

The proposed specifications for a number of impurities/degradants in the drug substance and drug product of Javlor are above the qualification thresholds stated in the ICH Guidelines Q3A(R) and Q3B(R)[9].

The sponsor submitted repeat dose toxicity studies with batches of vinflunine containing enhanced levels of impurities ("spiked batches") and *in vitro* genotoxicity studies with relatively pure batches of each of the impurities.

Although concentrations used in the bacterial mutagenicity assays were below 5000 mg/plate generally required, they were higher than 250 mg/plate, a threshold that detects 85% of mutagens (Kenyon *et al*, 2007[10]) and might be considered adequate in this instance. All compounds were negative in the bacterial mutagenicity assay but were clearly clastogenic in mammalian cells (mouse L5178Y ($TK^{+/-}$) lymphoma cells). Four compounds were considered clastogenic in both the presence and absence of metabolic activation, while another was only clastogenic in the absence of metabolic activation. As the parent compound vinflunine was also genotoxic, these findings do not raise additional concerns.

Repeat-dose toxicity studies with spiked batches of vinflunine were of 5 to 28 days duration in rats. A 14 day recovery period was included in some of these studies. No novel toxicities were apparent in animals treated with spiked batches of vinflunine but an increased incidence and severity of haematuria was seen in rats that received spiked batch, suggesting an exacerbation of renal toxicity. Based on findings in other studies, these enhanced renal effects may be attributed to one of the clastogenic compounds. However, as there were no obvious histopathological effects and the findings occurred at 4 times the maximum anticipated clinical dose on a mg/m^2 basis, the proposed specification for this compound is the same as for unspecified impurities, and given the intended patient population, the proposed limit in the drug substance may be considered acceptable. The proposed specifications for other impurities/degradants in the drug substance and/or drug product have been toxicologically qualified. Therefore, there are no objections on toxicological grounds to the proposed limits for related substances.

Nonclinical Summary and Conclusions

- The overall quality of the nonclinical part of the submitted dossier was high, and there were no major deficiencies.

- *In vitro*, vinflunine bound to tubulin, inhibited tubulin polymerisation, arrested mitosis and was cytotoxic to a number of cancer cell lines. Vinflunine showed some efficacy in murine tumour-bearing models; however only limited data were submitted to support the proposed indication. Cells over-expressing P-glycoprotein were resistant to vinflunine and other vinca alkaloids. The major human metabolite, 4-O-deacetylvinflunine, showed comparable *in vitro* and *in vivo* efficacy.

- The only clinically-relevant inhibitory activity observed in a receptor screening assay was at the mammalian opiate (non-specific) and μ-opioid receptors.

[9] *Impurities in New Drug Product* and *Impurities in New Drug Substance*. See http://private.ich.org/cache/compo/363-272-1.html

[10] Kenyon, MO *et al* (2007) An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. *Reg Toxicol Pharmacol* **48;** 75-86

- Safety pharmacology studies covered the full spectrum of major systems. With the exception of haematuria in repeat dose toxicity studies, there were no remarkable renal or gastrointestinal findings. Clinical signs of CNS toxicity (piloerection and prostration) were seen in rodents at doses which resulted in maximum blood concentrations below the clinical C_{max}. Inhibition of hERG K^+ channels and QT interval prolongation were seen at clinically-relevant concentrations. Other ECG abnormalities, reduced cardiac output and heart rate along with respiratory depression are all consistent findings with vinca alkaloids.

- Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Elimination half-lives were long in all species. Vinflunine was taken up into blood cells, plasma protein binding was moderate and tissue distribution was wide. In all species, vinflunine was extensively metabolised through both oxidative and hydrolytic pathways. CYP3A4 was the major oxidative enzyme while various esterases form the major mouse and human metabolite, 4-O-deacetylflunine. Drug-related material was excreted predominantly in the faeces of all species.

- There was no clinically-significant inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6, and no induction of CYP1A2, 2B6 or 3A4. As vinflunine is a substrate of CYP3A4 and
  P-glycoprotein, inhibitors or inducers of these are likely to affect the pharmacokinetic profile of vinflunine.

- Repeat-dose toxicity studies were performed in mice, rats and monkeys using the clinical route (IV). Overall, exposures achieved in animal studies were subclinical, due to a high order of toxicity with this compound. Toxicological effects were similar to those reported for other vinca alkaloids and consisted mainly of hepatotoxicity and bone marrow toxicity. Haematological changes (neutropenia and anaemia) subsequent to the bone marrow effects were also a feature of toxicity studies.

- Vinflunine was not mutagenic in a bacterial mutation assay but was mutagenic and clastogenic in mammalian systems (*in vitro* and *in vivo*). No carcinogenicity studies were submitted.

- Decreased sperm viability and motility were seen in male rats treated with doses resulting in twice the clinical AUC. Vinflunine administered during the period of organogenesis was embryofetotoxic and teratogenic in rats and rabbits. In a pre/postnatal study in rats, postnatal survival and body weight gain of pups were reduced. Effects on the reproductive organs were seen in both sexes, with small and soft testes in males and uterine changes compromising fertility in females. Some females did not progress through puberty.

- Reactions at the injection site included erythema, slight oedema and sores in rabbits with haematomas, perivenous collagen degradation and fibroplasia in monkeys.

- The pharmacology and toxicity of the major human metabolite, 4-O-deacetylvinflunine were similar to the parent compound.

- The specifications of 6 structurally-related impurities have been adequately justified by submitted data.

CONCLUSIONS AND RECOMMENDATIONS

As with other anticancer agents, relatively high toxicity of vinflunine was observed in nonclinical studies at exposures similar to those expected at the proposed clinical dose. The toxicities of particular note include cardiotoxicity, hepatotoxicity, bone marrow toxicity with subsequent haematological changes and local reactions at the injection site. Overall the data submitted suggested vinflunine ditartrate has a similar toxicity profile to the currently registered vinca alkaloids indicated for anti-neoplastic indications. There are no objections on nonclinical grounds to the registration of vinflunine ditartrate.

IV. Clinical Findings

Introduction

Aspects of development

The clinical development program of vinflunine consisted of pharmacokinetic studies (distribution, excretion, metabolism, dose proportionality, special populations, drug-drug interactions and safety/interaction studies), pharmacodynamic studies, and efficacy and safety 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 (non-small cell lung cancer (NSCLC))

- 1 ongoing Phase II study (metastatic breast)

- 1 Phase II study in gastric cancer (premature termination)

Studies in combination therapy included the following:

- 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 transitional cell carcinoma urothelium (TCCU)

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

- 3 Phase I studies (VFL 981, VFL 991, VFL 992)

- 2 Phase II studies (VFL202, CA 001)

- 1 randomised Phase III study (VFL 302)

GCP aspects

The sponsor stated that the clinical trials were performed in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Introduction

The clinical pharmacokinetics of vinflunine were evaluated in patients with a variety of malignancies. The tumours of the patients who participated in the Phase I/II clinical trials included several types of solid tumours, such as bladder cancer (Urothelial Transitional Cell Carcinoma of Urothelium, TCCU), NSCLC and breast cancer.

The clinical pharmacology studies with Vinflunine are listed in Tables 4 and 5 below.

Table 4: 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 5: 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
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
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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

Methods

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

1) 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. High-performance liquid chromatography (HPLC) methods were generally used for controls.

2) Methods for non-radiolabelled detection, used to assess unchanged VFL and its metabolites in biological fluids included HPLC/UV and LC/MS-MS (a HPLC method followed by tandem mass spectrometry detection). Both HPLC/UV and LC/MS-MS methods were developed and validated according to GLP.

Absorption

Not applicable to an IV formulation.

Distribution

A sharp decay in VFL blood concentrations immediately after the end of infusion was observed and illustrated the very rapid distribution from blood to tissues, supported by the large volume of distribution in humans: 35 ± 9 L/kg for Vdz and 19 ± 6 L/kg for Vss. 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

Pharmacokinetic (PK) parameters of VFL obtained in early dose finding Phase I studies are summarised in Table 6.

Table 6: Vinflunine pharmacokinetic parameters in blood from early Phase I studies

Study	Schedule of administration [dose range]	Number of patients	Sampling time period	Mean ± s.d. (CV%) Cl_{tot} (L/h) (CV)	V_{ss} (L) (CV)	Vd_z (L) (CV)	$T_{½z}$ (h) (CV)
9 L0070 98 IN 101 Q0	Once every 3 weeks [30 – 400 mg/m²]	30	96 h	**41.4 ± 12.9 (CV = 31%)**	833 ± 318 (CV= 38%)	1517 ± 503 (CV = 33%)	25.5 ± 3.9 (CV = 15%)
9 L0070 99 IN 101 Q0	Weekly [120 – 250 mg/m²]	14 pre-treated	168 h	**41.3 ± 8.85 (CV = 21%)**	1295 ± 416 (CV=32%)	2317 ± 649 (CV = 28%)	38.8 ± 6.62 (CV = 17%)
		20 chemonaive		**49.3 ± 10.8 (CV = 22%)**	1460 ± 512 (CV=35%)	2645 ± 712 (CV = 27%)	37.5 ± 6.30 (CV = 17%)
9 L0070 99 IN 102 Q0	Days 1 and 8 every 3 weeks [170 – 210 mg/m²]	15	168 h	**39.1 ± 10.0 (CV = 26%)**	1167 ± 320 (CV=27%)	2223 ± 602 (CV = 27%)	40.3 ± 9.63 (CV = 24%)

Consistent values of VFL clearance in blood (ranging from 39.1 ± 10.0 to 49.3 ± 10.8 L/h) were calculated across studies. These values were in agreement with the typical value estimated close to 40 L/h in a population pharmacokinetic (PK) analysis. The terminal half-life of VFL was estimated to be approximately 40 h over a 168-h sampling period.

Inter-patient variability in VFL total clearance (Cltot) was moderate with similar CV (ranging from 21% to 31%) observed between studies (see Table 6). A more consistent estimate of inter-patient variability was obtained when pooling data from early Phase I studies as well as by population PK approach (see Table 7). Population PK analysis also enabled estimation of the intra-patient variability from the first up to the fourth administrations.

Table 7: Vinflunine clearance in blood and variabilities

	Pool of early Phase I data studies	First population PK model *[Study IRPF L00070-20127]* See 2.7.6, see file	Global PK population study *[Study IRPF 22284]* See 2.7.6, see file	
		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* (hepatic microsomes, hepatocytes cultures, insect transfected cells) and *in vivo* studies. A total of 11 metabolites were detected in blood, urine and faeces.

Seven 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)

The 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.

DVFL was the main circulating metabolite in blood and was both slowly formed and eliminated. A plateau of DVFL concentration was achieved about 12 h after VFL dosing; then the concentrations of DVFL declined slowly. Due to this particular profile, the peak concentration was observed at variable times: mean values of T_{max} across studies were between 10.8 h and 16.1 h with CV ranging from 60% to 109%.

The elimination phase of DVFL concentrations is likely to be characterised by a monoexponential decay. Similar values of half-life were obtained between studies (ranging from 91.7 h to 134 h) regardless of the high percentage of extrapolated DVFL area under the concentration-time curve from time zero to infinity (AUC_{inf}) (> 15-20%). DVFL data after repeated dosing (weekly or Days 1 and 8 dosing every 3 weeks) were adequately described by simulated profiles based on the first dosing estimated half-life. Therefore, the best estimate of DVFL half-life consistent between repeated dosing simulations and estimated values in each clinical study was approximately 120 h.

Dose proportionality and time dependency

The objectives of a Phase I pharmacokinetic (PK) study of vinflunine given as a 10-minute infusion every 3 weeks (Study 9 L0070 98 IN 101 Q0) were to determine the maximum tolerated dose (MTD) and the recommended dose (RD) (as primary objectives) and to explore the PK profile (among the secondary objectives) of VFL in patients after administration of VFL once every 3 weeks (D1 q3w). Ten dose levels of VFL from 30 mg/m² up to 400 mg/m² were administered and PK assessment was performed in 30 patients.

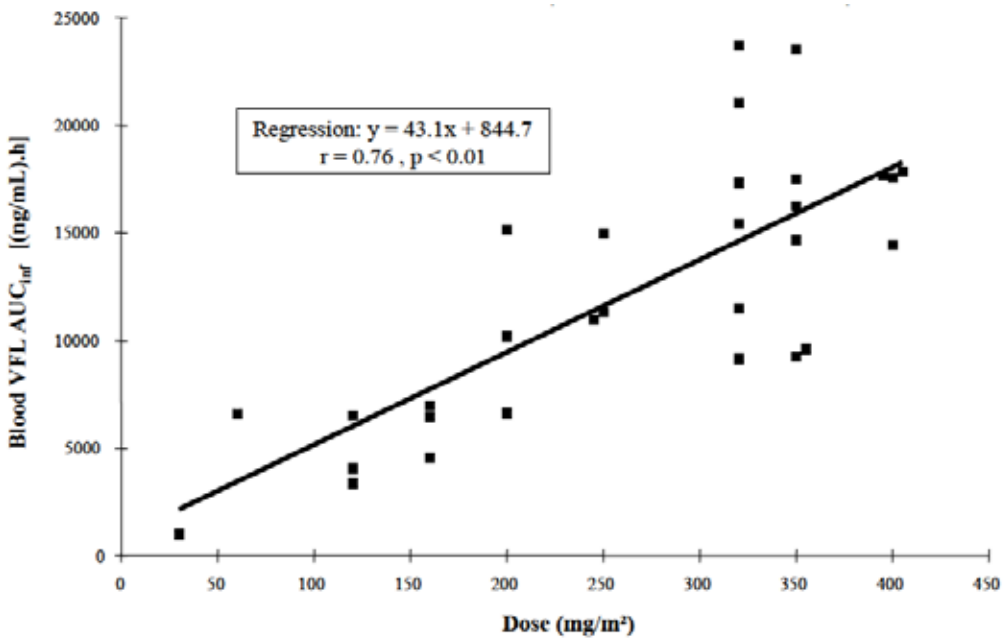
VFL blood concentrations versus time profiles were characterised by a sharp concentration decrease over the first 30 minutes following the end of infusion and then demonstrated a slower distribution /elimination phase.

An AUC versus dose proportional increase relationship was demonstrated for VFL (see Figure 1) and DVFL. For VFL, blood concentration exposures (that is, AUC_{inf} and AUC_{last}[11]) normalised to the dose, total body clearance (Cltot), $t_{½}$ z and renal clearance (Clr) showed no statistically significant differences between dose levels, from 30 mg/m² up to 400 mg/m². Likewise, DVFL metabolic ratio (MR) was independent of the dose level and DVFL AUC_{last} increase was proportional to the dose level.

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%. VFL 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.

[11] The area under the concentration-time curve from time zero to the end of the dosing interval (last) at steady state.

Figure 3: Relationships between vinflunine AUC_{inf} and dose (mg/m²) after the first IV vinflunine administration (n = 30 observations)



Excreted amount of VFL in urine was 11.2 ± 3.8% of the administered dose during the first 48 hours post-dosing and the renal clearance was 5.3 ± 2.7 L/h (approximately 13% of the blood total clearance).

For DVFL, the mean $t_{½}$ z value was 113 ± 66.9 h and the mean MR (calculated as the ratio of AUC_{last} DVFL/ AUC_{last} VFL) was 0.223 ± 0.087. The fraction of DVFL excreted in urine during the first 48 h post-dosing (expressed in equivalent of VFL) was less than 3% of the administered dose.

In summary, VFL and DVFL pharmacokinetics were linear over a range of VFL dose from 30 mg/m² up to 400 mg/m². VFL exhibited a high total clearance and a large volume of distribution. DVFL was the major circulating metabolite and demonstrated a slow formation and a slow elimination.

Intra- and inter-individual variability

Standard VFL PK parameters were 40 L/h, 40 h and between 2200 to 2600 L for Cltot, $t_{½}$ z and Vdz, respectively. Results obtained from Phase I trials and from population analyses were consistent and demonstrated a moderate inter-patient variability close to 25% and a small intra-patient variability close to or below 10% for VFL clearance. DVFL was the major metabolite observed in blood with a metabolic ratio between 0.30 and 0.50. It was slowly formed (T_{max} between 10.8 h and 16.1 h) and slowly eliminated (T½ z H 120 h). Inter-patient variability in blood exposure was estimated to be slightly higher for DVFL than for VFL: 31% *versus* 25%.

Special populations

Hepatic impairment

A Phase I pharmacokinetic dose adjusted study of IV vinflunine in cancer patients with liver dysfunction was conducted (Study IRPF L00070 IN 104 Q0). The objectives were to assess the effect of varying degree of liver impairment (LI) on VFL and DVFL PK and to propose

dose-adjustment guidelines if needed. Patients with LI were treated with VFL infused over 10 min once every 21 days.

VFL PK parameters were not statistically different between groups with LI and between LI groups and the control group (see Table 8) and all individual values from LI group were within the range of control values.

Table 8: Comparison on vinflunine pharmacokinetic parameters (mean ± standard deviation (s.d.)) between groups of liver impairment and control group

Groups of LI (dose in mg/m²)	VFL dose (mg/m²)	Nb of Patients	AUC_{inf} adjusted to 320 mg/m² (h.ng/mL)	Cl_{tot} (L/h)
Mild	320 (RD)	6	12175 ± 4556	48.8 ± 9.90
Moderate	320 (MTD)	3	15190 ± 4051	39.8 ± 14.5
	250 (RD)	6		
Severe	250 (MTD)	3	13627 ± 4045	47.6 ± 15.5
	200 (RD)	7		
Control group*	[120 – 250]	49	13844 ± 3605	43.9 ± 10.8
		ANOVA test (α = 5%)	0.40 (NS)	0.34 (NS)

MTD: Maximal tolerated dose, RD: Recommended dose
NS: not significant
*: Patients from 9 L0070 99 IN 101 Q0 and 9 L0070 99 IN 102 Q0 studies.

No significant correlation was observed between individual values of VFL clearance and each continuous biological variable at baseline (that is, bilirubin, AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), plasma total protein and prothrombin time), and between VFL clearance and the presence or absence of cirrhosis. Likewise, no difference was detected between grades of Child-Pugh liver disease classification in patients with cirrhosis.

Similarly, DVFL PK parameters (that is, $AUC_{0\text{-}168\ h}$[12] adjusted to 320 mg/m² and MR) were not statistically different between groups of LI and between LI groups and the control group.

No modification of vinflunine and DVFL pharmacokinetics was observed in patients presenting varying degrees of hepatic impairment, compared to patients with normal hepatic function. However, in the Australian Product Information dose adjustments are recommended in patients with Level 2 or 3 liver impairment.

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.

Renal impairment

A pharmacokinetic study of IV vinflunine in cancer patients with renal impairment is ongoing (Study IRPF L00070 IN 113 Q0); an interim analysis was provided. The objectives are to assess the effect of renal impairment on VFL and DVFL PK and to propose dose adjustment guidelines if needed. Patients with renal impairment (RI) were treated with VFL infused over 20 min once every 21 days for at least 2 cycles. Two groups of renal impairment were defined according to the baseline value of creatinine clearance (CLcr calculated by

[12] the area under the concentration-time curve calculated by linear trapezoidal rule from time zero to 168 h

Cockcroft-Gaul formula): Group 1 (moderate renal impairment) with 40 mL/min ≤ CLcr ≤ 60 mL/min and Group 2 (severe renal impairment) with 20 mL/min ≤ $CLcr_e$ < 40 mL/min.

This is an ongoing study. Twenty-two patients for Cycle 1 (13 in Group 1 and 9 in Group 2) were evaluable for PK assessment as of the cut-off date (30 April 2007) of the interim analysis.

VFL Cl_{tot} was significantly decreased in patients with RI compared to those of the control group (see Table 9). There was a mean decrease of 16% and 30% for moderate and severe RI groups, respectively.

Table 9: Comparison of vinflunine and 4-O-deacetylvinflunine pharmacokinetic parameters (mean ± s.d.) between groups of renal impairment and control group

Parameter		Control group (Cycle 1, n = 118)	Moderate renal impairment group (Cycle 1, n = 13)	Severe renal impairment group (Cycle 1, n = 9)	GROUP effect (ANOVA)
VFL	Cl_{tot} (L/h)	42.9 ± 10.4	35.9 ± 8.0	29.9 ± 6.10	p < 0.001
DVFL	MR DVFL AUC_{last} / VFL AUC_{last}	0.32 ± 0.08°	0.37 ± 0.13	0.31 ± 0.09	NS

NS: not significant.
°: For DVFL, control group made of 44 patients.

For DVFL, the MR (calculated as the ratio of DVFL AUC_{last} over VFL AUC_{last}) showed no statistically significant difference between groups. This result combined with the strong correlation evidenced between AUCs of VFL and DVFL indicated that the effect of RI on exposure to DVFL was similar to the one on exposure to VFL.

The results of this interim analysis suggested that RI affected the elimination of both VFL and DVFL to a similar extent. The pharmacokinetic-guided dose adjustment proposed in this study allowed to obtain AUCs of VFL and DVFL corresponding to those expected at the recommended dose of 320 mg/m² in patients with $CLcr_e$ > 60 mL/min. Based on PK results and safety results observed after the first cycle, dosing recommendations in patients with RI are proposed as follows:

- moderate renal impairment (40 mL/min ≤ CLcr ≤ 60 mL/min):

VFL dose = 280 mg/m²;

- severe renal impairment (20 mL/min ≤ CLcr < 40 mL/min):

VFL dose = 250 mg/m².

Elderly patients

A pharmacokinetic study of IV VFL in elderly cancer patients (L00070 IN 114) started in January 2005 and is ongoing. No results were available at the time of this submission.

Gender, race, weight, elderly, children

No specific studies were submitted with regard to gender, race or weight. No specific studies in children were submitted. According to the population pharmacokinetic analysis, neither gender nor Performance Status (Eastern Cooperative Oncology Group (ECOG) score[13]) had an impact on vinflunine clearance which is directly proportional to body surface area.

[13] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease

Drug Interactions

Studies were carried out either *in vitro* or *in vivo* when combined chemotherapies were investigated in Phase I/II trials. The capability of VFL to induce or to inhibit CYP enzymes was evaluated *in vitro* on human hepatocytes or on microsomes.

VFL had no inducing effect on CYP1A2, CYP2B6 and CYP3A4 activity levels nor on the corresponding mRNA levels. Similarly, VFL had no significant inhibition effect on CYP isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4).

An *in vitro* Drug-Drug Interaction *(*DDI) study focused on CYP3A4 was carried out with 22 selected drugs. Ritonavir and ketoconazole, and more faintly itraconazole, docetaxel and paclitaxel are suggested to generate DDI when combined with VFL. In a Phase I study with a fixed dose of ketoconazole (400 mg/D x 8D) and with VFL dose escalations (BMS CA 183009), a 30% decrease of VFL total clearance was observed, resulting in a 30% increase of both VFL and DVFL AUCs. Thus combining strong CYP3A4 inhibitors with VFL represents a real risk of VFL over-exposure if the usual recommended dose is administered. Such combined treatment should be avoided when possible. If not, an initial 50% VFL dose-reduction could be proposed with further moderate and cautious dose-escalation if the treatment is well tolerated.

Although no clinical study was conducted with strong inducers, the opposite impact to that from inhibitors may be anticipated, resulting in low VFL exposures. Such associated treatments should be excluded. If not, a risk of lower efficacy might exist because increasing VFL dose to compensate for the exposure decrease due to induction might increase the risk of adverse effects.

Risk of DDI was also assessed in VFL combined chemotherapy with cisplatin (CDDP) (IRPF L00070 IN 105J1), with carboplatin (CBDCA) (IRPF L00070 IN 107J1), with liposomal doxorubicin (IRPF L00070 IN108J1), with doxorubicin (IRPF L00070 IN 111B0), with capecitabine (IRPF L00070 IN 109B0), and with gemcitabine (IRPF L00070 IN 106J1). The last three studies are still ongoing while the first 3 are completed. No mutual DDI were observed for CDDP, CBDCA, capecitabine and gemcitabine.

In relation to doxorubicin (DOXO), a study of the 3-weekly schedule is completed and reported while evaluation of the D1, D8 q3w schedule is ongoing. From the pharmacokinetic evaluable patients (14 for VFL and 15 for DOXO) no major modification was observed compared to the control group (n=79). An apparent decrease of VFL Cltot mean value (47.7 L/h versus 35.7 L/h) was suggested when increasing the DOXO-combined dose from 40 to 50 mg/m² but this might be due to the small number of patients per dose level (6 and 8) since the range of values overlapped (29-61 versus 22-44 L/h) and were within the range of control values (mean 42 L/h and range 20-74 L/h). Both VFL and DOXO are mostly metabolised through CYP3A4, hence an impact on doxorubicinol would have been observed in case of

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affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead

substrate competition on this isoenzyme whereas no modification was observed for DVFL, doxorubicin or doxorubicinol.

In relation to liposomal doxorubicin (PLDH-DOXO) a DDI was noted on both tested schedules of VFL (3 weeks and D1, D8 q3w). For a given VFL dose, the VFL exposure increased by 15 – 30% when the combined dose of PLDH-DOXO was increased, and conversely Cltot decreased whereas neither Vdz, T1/2z nor DVFL AUCs appeared to be affected. Concerning PLDH-DOXO and for a given dose, the AUC of total DOXO was about 2-fold decreased when the combined VFL dose was increased. Both Cltot and volume of distribution at steady –state (Vss) were about 2-fold increased whereas $t_{½}z$ and doxorubicinol AUCs were little affected. These data suggest that the CYP3A4 pathway was not concerned in this DDI that was more probably related to the drug distribution in the blood. Liposomal DOXO is mostly located in the blood compartment while VFL is mostly located in tissues, as indicated by their respective volumes of distribution. If VFL (MM = 885) is trapped in blood by adsorption onto PLDH liposomes, its blood concentration will increase and its clearance calculated from blood AUC will decrease. The consequence of such a mechanism would be limited since blood represents a small fraction of VFL Vd (about 0.2%) and therefore very little drug will be transferred from tissues to blood. Blood total concentrations were decreased, clearance calculated on blood AUC was increased and so was Vd. Doxorubicinol production was minimally affected, indicating that distribution was the likely origin of the modifications. In the clinical study, there was no relationship between the occurrence of dose limiting toxicities (DLTs) and overexposure to DOXO or VFL.

Overall, risks of DDI with VFL are very likely with strong inhibitors or strong inducers of CYP3A4. There are more limited risks with liposomal doxorubicin, and interactions are unlikely or not clinically significant with platinum, doxorubicin, capecitabine and gemcitabine.

Evaluator's overall conclusions on pharmacokinetics

Studies have shown that VFL was metabolised at a low and variable rate: 10-44% in human microsomes and 6-31% in human hepatocytes. Unchanged VFL was the major observed compound representing about 80% of total peak area and up to 9 HPLC metabolite peaks were detected. The metabolism pattern was qualitatively comparable between microsomes and hepatocytes models. The most abundant HPLC metabolite peaks by order of decreasing importance were P8VFL/P9VFL (about 7%), followed by P13VFL/P14VFL, P6VFL and P11VFL (1.4-5.5%). In clinical trials, unchanged VFL achieved the highest concentrations and three metabolite HPLC peaks were detected in blood: P9VFL, P6VFL, and P11VFL. P9VFL (which was demonstrated to correspond to DVFL) was the main circulating metabolite and was slowly formed and slowly eliminated. Therefore, DVFL was still quantifiable after one week post-dosing, and P6VFL and P11VFL exhibited much lower concentrations and were rapidly eliminated during the first week after dosing.

Investigational studies using human biomaterials exclusively demonstrated that the metabolism of VFL was strongly correlated with CYP3A4 activity while DVFL was likely to be produced by esterases. The involvement of CYP3A4 in VFL biotransformation was confirmed *in vivo* after administration of VFL combined with ketoconazole.

During metabolite identification from clinical samples, bile was found to be a major route of elimination for the metabolites of VFL. A mass-balance elimination study showed that after 250 mg/m² 3H-VFL administration in 3 patients, bile was the predominant route of elimination with about 2/3 of the total radioactivity recovered in faeces over two weeks *versus* 1/3 in urine. Radioactivity was more rapidly eliminated through kidneys than through

bile. VFL and DVFL were the major compounds eliminated in both media. VFL was predominantly excreted in urine and accounted for 17.9% of the administered dose versus 7.65% in faeces.

DVFL exhibited a balanced elimination profile and represented about 12% of the administered dose in urine or faeces. Several other metabolites [hydroxy VFL isomer 1 (M6/7), hydroxy VFL isomer 2 (M3), VFL 3,6 ether (M2), desmethyl VFL (M4) and metabolite 815d (M13)] were mainly observed in faeces although some of them were also detected, in very low amount, in urine.

Pharmacodynamics

Introduction

No healthy subject pharmacodynamic (PD) studies were submitted for evaluation. All PD studies have been conducted in cancer patients.

Mechanism of action

Vinflunine is a novel microtubule inhibitor. It is the first bi-fluorinated agent obtained by semisynthesis using superacidic chemistry. Vinflunine was selected on the basis of its high level of *in vivo* antitumor activity against experimental tumour models. Vinflunine binds to tubulin, inhibiting its polymerisation into microtubules. It causes treadmilling suppression, disrupts microtubule dynamics, arrests cells in mitosis and induces cell death via apoptosis.

Vinflunine presents specific features that distinguish it from the other vinca alkaloids. Vinflunine binds relatively weakly to tubulin at the vinca-binding site. This has major implications in terms of predicting reduced neurotoxicity. The suggestion based on *in vitro* testing that vinflunine would be less neurotoxic than vinorelbine or vincristine has been confirmed so far. Vinflunine displays a wide spectrum of antitumor activity *in vivo* in various mouse models of human cancer. Concurrent and historical comparisons with vinorelbine and other classic vinca alkaloids showed that vinflunine exerts superior antitumor effects, both in terms of survival prolongation and tumour growth inhibition. Although vinflunine belongs to the group of multidrug resistance-associated antitumor agents it is a far less potent inducer of drug resistance than vinorelbine under identical selection conditions. In addition VFL exhibits vascular disrupting and antiangiogenic properties at doses considerably lower than those needed for vinorelbine.

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) (see Table 10 below). MTD and the RD were determined for each schedule of vinflunine administration: once every 3 weeks (on Day 1), weekly administration (on Day 1), and twice every 3 weeks (on Days 1 and 8).

Table 10: 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	-	-	-

Study VFL 981

Study design and objectives: This was a Phase I study, assessing the pharmacokinetics of vinflunine given as a 10 minute infusion once every 3 weeks in patients with advanced solid tumours. The study was a dose escalating, multicentre (3 centres in France), open-label, non-randomised trial. The study was carried out between 1December 1998 and 23 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 examine relationships between the pharmacokinetics of vinflunine and clinical toxicities and to assess antitumor activity in patients with measurable and/or evaluable disease. Vinflunine was given IV as a 10 minute infusion at a fixed dose and repeated every 21 days according to the observed toxicities.

Results: 31 patients were evaluable. The MTD of vinflunine administered in a 10 minute infusion every 3 weeks was 400 mg/m². The RD for further trials was 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 were shown to be linear with the administered doses. Inter-individual variability was moderate. Leucopaenia and neutropenia were correlated with vinflunine exposure.

Study VFL 991

Study design and objectives: This was a Phase I study, assessing the pharmacokinetics of vinflunine given as a 10-minute infusion on a weekly schedule to patients with various cancers. The study was a dose escalating, multicentre (3 centres - France, Switzerland, Belgium), open-label, non-randomised trial. The study was carried out between 4 October 1999 and 18 June 2003. The primary objective was to determine the MTD of vinflunine in cancer patients. Following Protocol Amendment 3 (12 April 2000) it was decided to separately determine 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, to examine relationships between the pharmacokinetics of vinflunine to clinical toxicities observed, and to assess anti-tumour activity.

Results: In Group A, 14 patients were evaluated at three dose levels of weekly vinflunine. The MTD was reached at 190 mg/m²/week and the RD established at 120mg/m²/week. In Group B, 26 chemonaive patients, the MTD was not determined even at the high doses (250 mg/m²) 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 (considered a DLT). No other significant modification in liver enzymes was seen. The recommended doses were associated with an acceptable tolerability profile, mainly consisting of mild nausea and vomiting, no severe neutropenia , and no thrombocytopenia or anaemia. Leucopaenia and neutropenia were correlated to vinflunine exposure.

Study VFL 992

Study design and objectives: 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 or a weekly schedule to patients with various cancers. The study was a dose escalating, multicentre (across France and the UK), open-label, non-randomised trial. The study was carried out between 21 October 1999 and 1 September 2000. The primary objective was to determine the MTD of vinflunine in cancer patients. 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 examine relationships between the pharmacokinetics of vinflunine and the observed clinical toxicities and to assess anti-tumour activity.

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

Secondary pharmacology

No studies were submitted for evaluation.

Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic properties of vinflunine were studied in cancer patient populations. The methodology and conduct of the studies to determine the optimally tolerated dose of vinflunine was satisfactory. 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.

Efficacy

Vinflunine is a novel microtubule inhibitor obtained by semi-synthesis using superacidic chemistry to selectively modify the catharanthine moiety of the vinca alkaloid molecule and optimise the therapeutic index of these derivatives. VFL blocks cells at G2/M phase and induces cell death via apoptosis (Pourroy B, 2004, Simoens C, 2006). *In vitro* VFL accumulates readily in the cell (Kruczynski A, 2002). VFL has the capacity to inhibit tubulin polymerisation, without any stabilising effect on assembled microtubules, at concentrations comparable to those of the other vinca alkaloids. VFL induced concentration-dependent reduction of the microtubular network of interphase cells, accompanied by paracrystal formation (Jean-Decoster,1999, Okouneva T, 2003).

In vivo antitumor activity of VFL, and its superiority over that of vinorelbine, was first identified against the murine IV -grafted P388 leukaemia and then confirmed in a series of murine and human 'solid' tumour xenografts (Kruczynski A,1998b, Hill B,1999). Clear dose-dependency and some schedule-dependency were noted. VFL significantly prolonged survival in five murine tumours, by factors ranging from 100 to 357%, and proved superior to vinorelbine.

Vinflunine demonstrated markedly superior tumour growth inhibition against a panel of 11 human tumours xenografted onto nude mice, with a 64% response rate reflecting high or moderate activity versus only 27% for vinorelbine (Kruczynski A,1998b, Hill B,1999).

The clinical development program for vinflunine in second-line treatment of patients with TCCU after failure with platinum-containing chemotherapy regimens included 3 Phase I studies (VFL 981, 991 and 992), 2 Phase II studies (VFL 202 and CA001) and 1 randomised Phase III study (VFL 302). Table 11 below summarises the Phase II/III studies. VFL 302 was nominated as the pivotal efficacy and safety study for the proposed indication.

Table 11: Summary of Phase II/III studies

Study N°	Desiga	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 studies and main clinical studies

Dose-response studies

Three Phase I studies 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 and 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/m^2 IV q3w. A strong correlation between vinflunine AUC and maximum neutrophil count decrease from baseline was demonstrated. Preliminary evidence of antineoplastic activity was documented (tumour responses were observed in 1 renal and 2 breast cancer patients).

Starting in October 2000, an international program of Phase II studies with vinflunine as a single agent was commenced in first, second and third line treatments 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 a 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 serious adverse event (SAE), including 4 (6.7%) 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, which was the dose subsequently used in clinical trials.

In May 2003, Study VFL 302 was initiated (discussed in detail below). This study started in 2003 and it took more than 3 years to recruit the required number of patients. After the first 10 patients were treated with vinflunine 320 mg/m² the following SAEs occurred and were promptly reported: febrile neutropenia in 2 patients and bone marrow depletion in 1 patient (Grade 4 neutropenia , Grade 3 thrombocytopenia and Grade 2 anaemia). All these patients had been previously treated with a standard chemotherapy (MVC, MVCarboplatin or CG), but although all of them were evaluated at study entry as having an ECOG/ World Health Organization (WHO) PS[14] of 1, they had presented with multi-organ involvement (some of them with more than 10 lesions) and a large tumoral burden.

A retrospective safety analysis of a Phase II trial (VFL 202; discussed below) was conducted in this relatively favourable Phase II population in second line patients with TCCU. Grade 3/4 neutropenia occurred in 57% of patients. Febrile neutropenia occurred only in 5 patients but these patients shared the same characteristics as the first patients included in the VFL 302 study. Three of them had PS 1 at entry and 2 out of 3 had received previous pelvic irradiation: moreover 9 out of 10 patients who were previously treated with radiation therapy to the pelvic area suffered from Grade 3/4 neutropenia . A relationship was therefore anticipated between the risk of developing severe haematological toxicity at the 320mg/m² VFL dose and certain specific baseline characteristics. It was concluded that patients with PS ≥ 1 or previous pelvic irradiation would be more prone to develop febrile neutropenia or to suffer from deleterious effects of the chemotherapy and so it was in the patient's best interest to tailor the dose level of the first administration of VFL. The dose recommendation was later further reduced to 280 mg/m^2 in patients at higher risk of myelosuppression (PS > 1, prior pelvic radiotherapy).

Main (pivotal) study

Study VFL 302

Study design and methods

This was a prospective, open-labelled, randomised, multicentre Phase III study in patients with advanced TCC of urothelial tract previously treated with a platinum-containing chemotherapy as first line treatment. Patients were randomised 2:1 to treatment with either VFL+ Best Standard of Care (BSC) or BSC alone. Per protocol, randomisation was to be stratified by study site and by best response to previous chemotherapy regimen (non-refractory and refractory patients). Refractory patients were those patients who had progressed within the first 2 cycles of chemotherapy administered in the first line setting. Prior to Amendment 1 of the protocol (19 November 2003), all patients randomised to the VFL+BSC group were treated with 320 mg/m² every 21 days as a 20-minute infusion. After Amendment 1, patients with an ECOG/WHO PS of 0 and without previous irradiation of the pelvic area received VFL IV 320 mg/m² plus BSC. Patients with ECOG/ WHO PS of 1 and patients with ECOG/ WHO PS of 0 with previous irradiation of the pelvic area received VFL as follows:

[14] WHO performance scale: The World Health Organisation (WHO) designed the scale which has categories from 0 to 4 as follows: 0 : fully active and more or less as you were before your illness, 1 - cannot carry out heavy physical work, but can do anything else, 2 - up and about more than half the day; you can look after yourself, but are not well enough to work, 3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself, 4 - in bed or a chair all the time and need a lot of looking after

First cycle: VFL IV 280 mg/m² plus BSC

Starting from Cycle 2: patients without haematological toxicities causing a treatment delay received VFL IV 320 mg/m² plus BSC. Patients with haematological toxicities causing a treatment delay received VFL IV 280 mg/m² plus BSC.

BSC was given according to institutional standards (including palliative radiotherapy, antibiotics, analgesics, steroids, transfusion). Dose modification and dose delays of VFL were allowed per protocol. No dose re-escalation was allowed after a dose reduction.

A cycle was defined as a 3-week period between 2 administrations of VFL (Day 1 of the cycle) or scheduled visit to the hospital (for patients in the BSC group). In the VFL+BSC group, treatment was administered until documented progression, unacceptable toxicity, or subject refusal. In the BSC group, visits were recorded until an inability to meet the 3-week schedule, progressive disease requiring systemic anticancer therapy, or subject refusal.

Primary objective

The primary objective was to compare survival in patients with advanced TCC of urothelial tract previously treated with a platinum-containing chemotherapy as first line treatment receiving either VFL+BSC or BSC alone.

Secondary objectives

The secondary objectives in the protocol were:

- to compare patient benefits through a quality of life questionnaire: European Organization for Research and the Treatment of Cancer (EORTC QLQ-C30) (Aaronson NK, 1993[15]) and clinical benefit parameters,
- to compare the safety profiles in both groups,
- to assess response rate, time to first response, duration of response and progression free survival in the VFL+BSC group.

Study participants

Inclusion criteria were as follows***:***

- Written informed consent must have been obtained and documented prior to beginning specific procedures for study and follow-up,
- Histologically proven TCC of the urothelial tract; locally advanced or metastatic disease,
- Patients with progressive disease who failed or progressed after first line platinum-containing chemotherapy for advanced or metastatic disease. First line chemotherapy was defined as receiving at least 2 cycles. Nevertheless, in case of clear evidence of progressive disease after the first 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 if affecting < 30% of the bone marrow and must have been completed 30 days before randomisation with full recovery of any related toxicity,

[15] Aaronson NK *et al* (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* **85**(5):365-76.

- Patients with measurable and/or non-measurable disease using response evaluation criteria in solid tumours (RECIST) (Therasse P, 2000) defined as:
  Measurable disease: Lesions that can be accurately measured in at least one dimension and which have not been previously irradiated:
  - assessed by conventional computed tomography scan (CT) scan: longest diameter (LDia) ≥ 20 mm,
  - assessed by spiral CT scan or magnetic resonance imaging (MRI): LDia ≥ 10 mm,

  Non-measurable disease: Lesions which have not 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 effusions, lymphangitis cutis/pulmonitis,
- Age ≥ 18 years,
- ECOG/WHO PS 0 or 1,
- Estimated life expectancy at least 12 weeks,
- Haematological function (before treatment initiation):
  - absolute neutrophil count ≥ 1.5 x 10^9/L,
  - platelets ≥ 100 x 10^9/L
- Hepatic function (before treatment initiation):
  - bilirubin ≤ 1.5 x upper limit of normal (ULN),
  - transaminases ≤ 2.5 x ULN (< 5 x ULN only in case of liver metastases)
- Renal function (before treatment initiation): calculated clearance of creatinine ≥ 40 mL/min (Cockcroft and Gault formula),
- ECG without significant modifications with clinical consequences (within 7 days before randomisation).

Exclusion criteria were as follows:

Patients meeting any of the following criteria were not eligible to participate in this study:

- Patients with non-TCC of the urothelial tract (adenocarcinoma, squamous cell carcinoma or other),
- Patients with known brain metastases or leptomeningeal involvement. Brain CT scans or MRI was not required to rule this out unless there was clinical suspicion of CNS involvement,
- Patients with peripheral neuropathy Grade ≥ 2 by NCI CTC (version 2.0) [16],
- History of serious or concurrent illness or uncontrolled medical disorder; any medical condition that could have been aggravated by treatment or which could not have been 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),

[16] National Cancer Institute Common Toxicity Criteria version 2.0. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

- patients with concurrent heart failure Class III-IV according to the New York Heart Association or patients with unstable angina pectoris, patients with myocardial infarction within 6 months and/or poorly controlled hypertension were excluded,

· Patients who had received more than one previous systemic chemotherapy for advanced or metastatic disease,
· Patients who had received neoadjuvant or adjuvant chemotherapy,
· Patients who had received any other investigational or anti-cancer therapy 30 days before randomisation,
· Patients with other malignancies except adequately treated basal carcinoma of the skin or *in situ* cervix carcinoma or incidental prostate cancer (T1a, Gleason score 6, prostate specific antigen < 0.5 ng/ml) or any other tumour with a disease free interval ≥ 5 years,
· Pregnant or lactating women,
· Men or women of child bearing potential not employing adequate contraception for the duration of the study and for 60 days after last treatment,
· Psychological, familial, sociological or geographical conditions which did not permit protocol compliance and medical follow-up.

The study population comprised men and women ≥ 18 years of age with histologically proven locally advanced or metastatic TCCU, documented progression after a platinum-containing regimen, and an ECOG/WHO PS of 0 or 1. The study was conducted globally across 83 centres in Canada, Europe, South Africa and Argentina.

Removal of patients from therapy or assessment

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).

Treatments

The study had two treatment arms: vinflunine (VFL) and Best Standard of Care (BSC) (Arm A) or BSC alone (Arm B).

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 (21 May 2003). The study duration phase was planned to continue until the last patients withdrew from the treatment (6 November 2006). After withdrawal from the study treatment, each patient would be followed until death.

Primary efficacy variable: Overall survival

The primary efficacy parameter was overall survival (OS) analysed in the whole randomised population. Survival was defined as the time elapsed from randomisation to death or date of last news (the last date of contact with the investigator was used for patients under treatment at the cut-off date). If a subject was not known to have died, the survival was censored at the time of last contact or at the date of the last news.

Secondary Efficacy Assessments

All analyses were performed on the randomised and evaluable patients based on the investigator's assessment. An independent review panel (IRP) confirmed all responses and time to response. All secondary analyses were performed according to the protocol on the VFL+BSC arm. Additional analyses on the BSC arm have been performed for the response, progression free survival (PFS), disease control, duration of stabilisation and duration of disease control. The following is a list of secondary efficacy assessments:

- best overall response rate: best confirmed complete response (CR) or partial response (PR) from the date of randomisation until end of treatment period,
- objective response rate: sum of CR and PR rate (using the best confirmed response recorded from the date of randomisation to the end of treatment),
- progression free survival (PFS): calculated from the randomisation date until the date of progression or death due to any cause (whichever came first).Patients who were lost to follow-up, or reached the time point of analysis without a known record of progression or death had the PFS censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occurred last,
- disease control rate: sum of CR, PR and stable disease (SD; SD lasting at least 12 weeks in the VFL+BSC group),

- time to first response: calculated among the responders (that is, CR and PR) from the randomisation date up to the date of first documented CR or PR later confirmed,
- duration of response: calculated among the responders (that is, confirmed CR and PR) from the time that measurement criteria are first met for CR or PR until the date of progression or death due to any cause, whichever occurred first.

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).

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 contact 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 the 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[17], Independent Review Committee

[17] RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer

(IRC) reviewed tumour assessments with CR and PR), time to response, response duration and progression free survival.

Statistical methods for categorical variables: The 2x2 test was performed to compare proportions. It was replaced by the 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 made 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 parameters. Confidence intervals on the median were calculated using the reflection method. Stratified Log rank 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.

Study populations analysed were as follows***:***

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

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

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 first line platinum-containing chemotherapy for advanced disease, 3) having received a neoadjuvant or adjuvant chemotherapy, 4) more than one 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 randomisation.

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 which 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: all treated patients were included (in the treatment arm they actually participated in).

patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments.

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 to which they were assigned by randomisation.

Analyses of efficacy

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 was performed based on blinded assessment by an Independent Review Panel (IRP) of patients with partial or complete responses or long stabilisations (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 randomised.

Results

Participant flow

As of the data cut-off date of 30 November 2006, 99% subjects in both groups were discontinued from the study and 1% in each group was still under treatment (see Table 12 below). The most common reasons for discontinuation were progressive disease (55%) in the VFL+BSC group and completion of the 18- week period (29%) and progressive disease (27%) in the BSC group.

Table 12: Subject Disposition: All Randomised Patients (M5, v84, p74)

	Number (%) of Patients	
Reason for treatment discontinuation	**VFL+BSC (N=253)**	**BSC (N=117)**
Under treatment at the cut off date	3 (1.2)	1 (0.9)
Completion of the 18-week period (BSC group)	NA	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 from protocol	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)

Recruitment

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

Conduct of the study

A total of eight protocol amendments were carried out. The most important amendments were as follows:

1) 19 November 2003

Initially, 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 ECOG/WHO 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.

According to the statistical analysis plan (SAP) 31 protocol deviations were established and 4 were considered as significant protocol deviations. A total of 116 (31%) patients had one 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 and it was the most common major protocol deviation (9% in both groups).

Baseline data

Baseline demographics were generally well balanced between the two treatment arms, with the exception of WHO performance status; 72% (VFL+BSC) versus 62% (BSC) had a PS status ≥ 1 (see Table 13). The majority of patients were men (78% in the VFL+BSC group, 81% in the BSC group) and the median age was 64 years. Baseline demographics were generally well balanced between the 2 VFL initial dose subgroups (280 mg/m² and 320 mg/m²). However, as expected, a higher proportion of patients in the 280 mg/m² subgroup compared with the 320 mg/m² were ≥ 65 years of age (51% versus 36%). Furthermore, as expected, a higher proportion of patients in the 280 mg/m² subgroup compared with the 320 mg/m² subgroup had a PS ≥ 1 (91% versus 15%). Also, a higher proportion of patients in the 280 mg/m² subgroup compared with the 320 mg/m² subgroup had received prior pelvic irradiation (28% versus 8%).

Table 13: 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 (37.1, 86.3)	64.2 (34.6, 85.0)
Age categories (n, %)		
< 50 years	23 (9.1)	9 (0.1)
≥ 50 years	230 (90.9)	108 (99.9)
<65 years	135 (53.4)	60 (51.3)
≥ 65 years	118 (46.6)	57 (48.7)
< 75 years	225 (88.9)	104 (88.9)
≥ 75 years	28 (11.1)	13 (11.1)
Gender at birth (n, %)		
Men	197 (77.9)	95 (81.2)
Women	56 (22.1)	22 (18.8)
WHO performance status (n, %)*		
0	72 (28.5)	45 (38.5)
1	181 (71.5)	72 (61.5)
Body weight (kg)	**N=253**	**N=116[a]**
Men		
Mean (s.d)	77.3 (13.5)	76.5 (11.9)
Median (min, max)	77.0 (38.7, 123.0)	76 (46.0, 110.0)
Women		
Mean (s.d)	64.3 (12.7)	68.5 (9.5)
Median (min, max)	61.5 (49.0, 120.0)	67.0 (49.0, 88.0)
Body surface area (m^2)	**N=253**	**N=116[b]**
Men		
Mean (s.d)	1.9 (0.2)	1.9 (0.2)
Median (min, max)	1.9 (1.4, 2.5)	1.9 (1.5, 2.3)
Women		
Mean (s.d)	1.7 (0.1)	1.7 (0.1)
Median (min, max)	1.7 (1.5, 2.3)	1.7 (1.4, 2.0)
Haemoglobin levels at baseline (NCI CTC)	**N=246[c]**	**N=111[c]**
Grade 0	120 (48.8)	62 (55.9)
Grade 1	91 (37.0)	37 (33.3)
Grade 2	34 (13.8)	12 (10.8)
Grade 3	1 (0.4)	0

Table 13 continued: Baseline Characteristics: All Randomised Patients

Alkaline phosphatase levels at baseline	**N=241[d]**	**N=108[d]**
Grade 0	167 (69.3)	72 (66.7)
Grade 1	58 (24.1)	23 (21.3)
Grade 2	10 (4.1)	6 (5.6)
Grade 3	1 (0.4)	3 (2.8)
Not assessed at baseline	5 (2.1)	4 (3.7)
Creatinine clearance at randomisation (mL/min)	**N=248[e]**	**N=117**
< 40	10 (4.0)	4 (3.4)
40 - <60	104 (41.9)	41 (35.0)
≥60	134 (54.0)	69 (59.0)
Not assessed at baseline	0	3 (2.6)

* data extracted from randomisation form or clinical examination form if missing in the randomisation form
a: Patients 030403, 030405, 090103 weight is depicted in cycle 1 sheet; patient 030410 no data concerning weight.
b: Patient 030410 no data concerning weight and no BSA and for patient 030211 only the BSA and height were available at cycle 1 sheet.
c: evaluable population for haematology
d: evaluable population for biochemistry
e: all treated patients

All patients had received first line platinum-containing chemotherapy mainly for metastatic (advanced) disease except patients who received adjuvant or neoadjuvant chemotherapy (major deviation) (see Table 14). Gemcitabine/platinum-containing regimens were the most common regimens administered (75% VFL+BSC, 70% BSC). Slightly less than half of the patients in each arm had a CR or PR as their best response to their most recent platinum-containing regimen (49% in the VFL+BSC group, 44% in the BSC group).

The two arms were well balanced with respect to other prior therapies (see Table 15). However, a higher proportion of patients in the VFL+BSC arm compared with the BSC arm had prior radiotherapy with palliative intent (24% versus 14%).

All patients had TCC as their primary tumour type at diagnosis (see Table 16). Pure transitional was the predominant histopathological cell type (91% VFL+BSC, 93% BSC). The primary tumour site for most patients was the bladder (79% VFL+BSC, 85% BSC). Slightly less than half of the patients in the VFL+BSC and BSC groups had stage IV disease at diagnosis (47% versus 45%).

Table 14: Summary of Prior Platinum Experience: All Randomised Patients

	Number (%) of Patients	
	VFL+BSC N (%)	BSC N (%)
Received a prior platinum-containing chemotherapy	**N = 253**	**N = 117**
For metastatic disease	250 (98.8)	111 (94.9)
Gemcitabine/platinum[a b]:	190 (75.1)	82 (70.1)
M-VAC[c]	34 (13.4)	14 (12.0)
CMV	16 (6.3)	8 (6.8)
Other platinum containing regimens[d]	10 (4.0)	7(6.0)
For neoadjuvant/adjuvant:	3 (1.2)	6 (5.1)
Gemcitabine/platinum[a]	2 (0.8)	5 (4.3)
M-VAC[c]	1 (0.4)	1 (0.9)
Other platinum containing regimens[d]	0	0
Received cisplatin, carboplatin or other platinum chemotherapy	**N = 253**	**N = 117**
Cisplatin (and no other platinum containing chemotherapy)	164 (64.8)	85 (72.6)
Carboplatin (and no other platinum containing chemotherapy)	75 (29.6)	23 (19.7)
Oxaliplatin (and no other platinum containing chemotherapy)	8 (3.2)	2 (1.7)
Several or any other platinum-containing chemotherapy	6 (2.4)	7 (6.0)
Best response to most recent prior platinum containing regimen	**N = 250[e]**	**N = 111[e]**
Complete response	27 (10.8)	8 (7.2)
Partial response	95 (38.0)	41 (36.9)
No change	63 (25.2)	33 (29.7)
Progressive disease	59 (23.6)	28 (25.2)
Not evaluable	6 (2.4)	0
Not applicable or missing	0	1 (0.9)

a: includes carboplatin + gemcitabine + vinblastine, gemcitabine + cisplatin/gemcitabine + carboplatin, gemcitabine + carboplatin, gemcitabine + carboplatin + herceptin, gemcitabine + cisplatin + carboplatin, gemcitabine + cisplatin + paclitaxel, gemcitabine + cisplatin + paclitaxel + carboplatin, gemcitabine + cisplatin + vinblastine + carboplatin, gemcitabine + oxaliplatin, gemcitabine + cisplatin, docetaxel + cisplatin + gemcitabine

b: patient 550306 received intravesical platinum and gemcitabine+cisplatin for metastatic disease

c: includes methotrexate + vinblastine + doxorubicin + cisplatin, methotrexate + vinblastine + epirubicin+ cisplatin, mitoxantrone + carboplatin + methotrexate + vinblastine

d: includes carboplatin + doxorubicin, carboplatin + methotrexate + vinblastine, carboplatin + paclitaxel, methotrexate + cisplatin, epirubicin + cisplatin + methotrexate + vincristin, mitomycin c, methotrexate + vinblastine + carboplatin + (doxorubicin or cisplatin), docetaxel + cisplatin, cyclophosphamide + cisplatin

e: calculated only for patients receiving prior platinum containing chemotherapy for metastatic disease

Table 15: Other Prior Therapies: All Randomised Patients

	Number (%) of Patients	
	VFL+BSC (N=253)	BSC (N=117)
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)
Intent of radiotherapies		
Concomitant with chemotherapy only	0	1 (0.9)
Curative only	10 (4.0)	7 (6.0)
Curative + palliative	3 (1.2)	2 (1.7)
Palliative only	60 (23.7)	16 (13.7)
Prophylactic only	0	2 (1.7)
Prophylactic + palliative	1 (0.4)	0
Immunotherapy	27 (10.7)	9 (7.7)
Intent of immunotherapy		
Unknown	2 (0.8)	1 (0.9)
Adjuvant	23 (9.1)	8 (6.8)
Maintenance	2 (0.8)	0

Table 16: Tumour Characteristics at Diagnosis: All Randomised Patients

	Number (%) of Patients	
	VFL+BSC (N=253)	BSC (N=117)
Primary tumour type		
Transitional cell carcinoma	253 (100.0)	117 (100.0)
Primary tumour site		
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)
Histopathological type		
Pure transitional	230 (90.9)	109 (93.2)
Mixed with squamous cell	14 (5.5)	6 (5.1)
Mixed with glandular differentiation	5 (2.0)	2 (1.7)
Squamous and glandular metaplasia	3 (1.2)	0
Other	1 (0.4)	0
Number of target lesions		
No target lesions	18 (7.1)	9 (7.7)
1	54 (21.3)	30 (33.3)
2 - 3	84 (33.2)	43 (25.6)
4 - 5	52 (20.6)	21 (17.9)
≥ 6	45 (17.8)	14 (12.0)
Sum of measurable target lesions (mm)	**N=235**	**N=108**
Mean (s.d)	108.9 (82.5)	93.4 (65.1)
Median (range)	86.0 (10.0, 536.0)	74.5 (0, 345.0)
Stage at diagnosis		
0a	12 (4.7)	3 (2.6)
0is	3 (1.2)	1 (0.9)
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)

Baseline disease characteristics were well balanced between the 2 treatment arms (see Table 17). The median time from initial pathological diagnosis to study entry was 1.5 years in the VFL+BSC arm and 1.6 years in the BSC arm; the median progression free interval after a platinum-based regimen was 1.8 months in the VFL+BSC arm and 2.3 months in the BSC arm. Fifty-nine percent of patients in both arms had progressed within 3 months of discontinuation of their first line regimen.

Table 17: Summary of Baseline Disease Characteristics: All Randomised Patients

	Number (%) of Patients	
	VFL+BSC (N=253)	**BSC (N=117)**
Time from initial diagnosis to study entry (years)		
Mean (s.d)	2.8 (3.3)	2.4 (2.6)
Median (min, max)	1.5 (0.2, 18.0)	1.6 (0.2, 15.8)
Progression free interval: time (months) from end of 1st line chemotherapy to relapse/progression	**N = 250[a]**	**N=108[a]**
Mean (s.d)	4.0 (6.7)	3.3 (3.9)
Median (min, max)	1.8 (0, 57.9)	2.3 (0, 27.7)
< 3	148 (59.2)	64 (59.3)
≥ 3	102 (40.8)	44 (40.7)
< 6	206 (82.4)	93 (86.1)
≥ 6	44 (17.6)	15 (13.9)
< 12	233 (93.2)	106 (98.1)
≥ 12	17 (6.8)	2 (1.9)
Treatment free interval (months): from end of prior chemotherapy to 1st dose of VFL for VFL+BSC or randomisation for BSC	**N = 245[b]**	**N = 111[b]**
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)
Time from relapse or progression after 1st line chemotherapy to randomisation (months)	**N=250[a]**	**N=108[a]**
Mean (s.d)	1.9 (3.5)	2.0 (3.4)
Median (min, max)	1.1 (0.2, 46.0)	1.0 (0.2, 29.9)
< 1	118 (47.2)	53 (49.1)
≥ 1	132 (52.8)	55 (50.9)
Refractory status at randomisation		
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)
Metastatic sites		
Lung (not liver, not bone)	53 (20.9)	23 (19.7)
Liver (not lung, not bone)	20 (7.9)	11 (9.4)
Bone (not lung, not liver)	36 (14.2)	12 (10.3)
Lung + liver	21 (8.3)	9 (7.7)
Lung + bone	26 (10.3)	7 (6.0)
Liver + bone	19 (7.5)	8 (6.8)
Lung + liver + bone	13 (5.1)	8 (6.8)
Lung, liver or bone	188 (74.3)	78 (66.7)
Visceral involvement[c]	187 (73.9)	87 (74.4)

a: The number of patients with data does not match the total for each group because the dates of relapse or progression after first line were missing for patients who did not receive a first line for advanced disease, or non applicable for three patients in the BSC arm who have never progressed after the first line chemotherapy (Patients No. 030206, 110504, 550644)
b: Only patients with first line treatment for advanced disease are considered
c: 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

Table 18 presents the data sets used in this study.

Table 18: Analysis Populations

	VFL+BSC		BSC		Total	
	N	%	N	%	N	%
All randomised	253	100.0	117	100.0	370	100.0
All treated[a]	248	98.0	117	100.0	365	98.6
Per protocol population[b]	244	96.4	107	91.5	351	94.9
Response evaluable as per investigator	215	85.0	93	79.5	308	83.2
After IRP: response evaluable	210	83.0	93	79.5	303	81.9

a: The all-treated population was used for safety analyses

b: Per protocol population excludes patients not treated, not treated in the group assigned by randomisation or who had 1 or more of 4 clinically significant deviations (more than 1 line of chemotherapy, no locally advanced or metastatic histologically proven TCC at study entry, no progression after 1st line platinum-containing chemotherapy for advanced disease and patients having received a neoadjuvant or adjuvant chemotherapy).

Table 19 presents the reasons why patients were not evaluable for response after IRP.

Table 19: Reasons Not Evaluable for Response After IRP

					Initial VFL Dose			
	VFL+BSC		BSC		280 mg/m²		320 mg/m²	
	N	%	N	%	N	%	N	%
Not treated and without any clinically significant deviation at baseline	5	11.6	0	0	NA	NA	NA	NA
Treated and with a clinically significant deviation at baseline	3	7.0	9	37.5	1	3.4	2	22.2
Not evaluable according to IRP	8	18.6	0	0	6	20.7	2	22.2
< 2 cycles because of (related) toxicity	6	14.0	0	0	2	6.9	4	44.4
< 2 cycles for other reason or still on study	12	27.9	7	29.2	12	41.4	0	0
Not assessed for another reason	9	20.9	7	29.2	8	27.6	1	11.1
Treated and with an on study major deviation	0	0	1	4.2	0	0	0	0
Number of patients	43	100.0	24	100.0	29	100.0	9	100.0

As was stated earlier, 31 protocol deviations were established. Four were considered as significant protocol deviations. A total of 116 (31%) patients had one or more protocol deviations: 73 (29%) in the VFL+BSC arm and 43 (37%) in the BSC arm. There were no clinically important differences between the two arms for the protocol deviations.

A total of 13 patients had at least one clinically significant protocol deviation at entry and one while on study (see Table 20). One patient (from the BSC group) had a significant deviation whilst on-study.

Table 20: Clinically Significant Protocol Deviation according to total number of deviations

Detail of significant Deviations	VFL+BSC N=253	BSC N=117
Patients with significant eligibility deviation		
More than 1 line of chemotherapy	1 (0.4)	0
No locally advanced or metastatic histologically proven TCC at study entry	1 (0.4)	1 (0.8)
No progression after 1st line platinum-containing chemotherapy for advanced disease	3 (1.2)	9 (7.7)
Patients having received a neoadjuvant or adjuvant chemotherapy	4 (1.6)	6 (5.1)
Patients with on-study protocol deviation		
Prohibited on-study concomitant therapy	0	1 (0.8)
Total number of patients with clinically significant protocol deviations	**4 (1.6)***	**10 (8.5)***

*Patients can present several reasons of deviations

The per-protocol population corresponds to the randomised population minus non-eligible patients. The per protocol populations therefore excluded 13 patients who had a significant deviation at baseline, one patient with a significant deviation during the study and five non-treated patients. The per protocol population comprised 244 patients in the vinflunine + BSC arm and 107 patients in the BSC arm.

Outcomes and estimation

Overall survival (OS) – All randomised patients

There was a 2-month median survival advantage favouring the VFL+BSC; 6.9 months versus 4.6 months. The risk of death was reduced by 12% in the VFL+BSC arm compared to the BSC arm: HR (95% CI) of 0.88 (0.7, 1.1) (see Table 21 and Figure 4); however the overall survival difference between both arms was not statistically significant (p=0.2868) in the whole randomised population. 81% patients died in the VFL+BSC arm and 88% died in the BSC only arm.

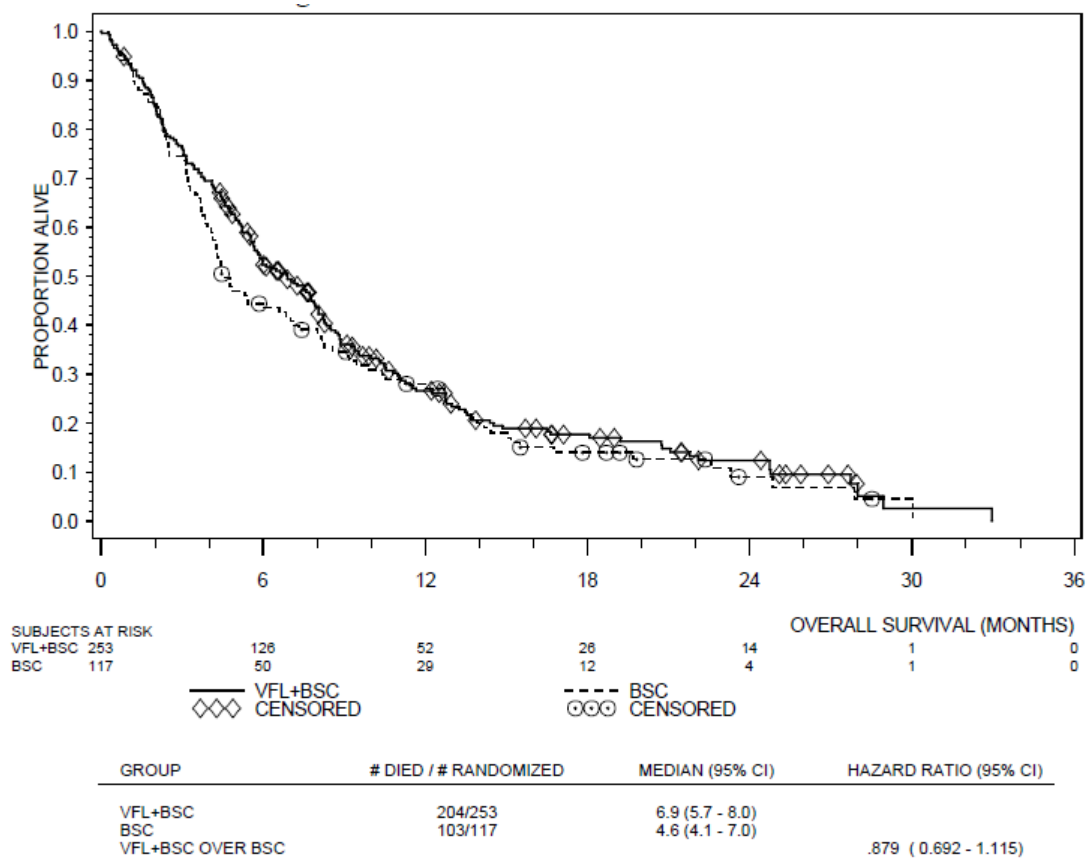
Overall survival data was updated 6 months after the first analysis in November 2006. OS in the all randomised population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus 4.6 months), with a reduction of risk of death by 12%, HR 0.88 (95% CI: 0.69, 1.10). This difference was not statistically significant (p = 0.2546).

Table 21: Overall Survival: All Randomised Patients

	VFL+BSC (N=253)	BSC (N=117)
No. of events	204	103
No. censored (%)	49 (19.4)	14 (12.0)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.6 (4.1, 7.0)
Hazard ratio (95% CI)	0.88 (0.69, 1.12)	
p value[a]	0.2868	

a: Stratified log rank test

Figure 3: Overall Survival: All Randomised Patients



GROUP	# DIED / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95% CI)
VFL+BSC	204/253	6.9 (5.7 - 8.0)	
BSC	103/117	4.6 (4.1 - 7.0)	
VFL+BSC OVER BSC			.879 (0.692 - 1.115)

Overall survival (OS) - Per protocol population

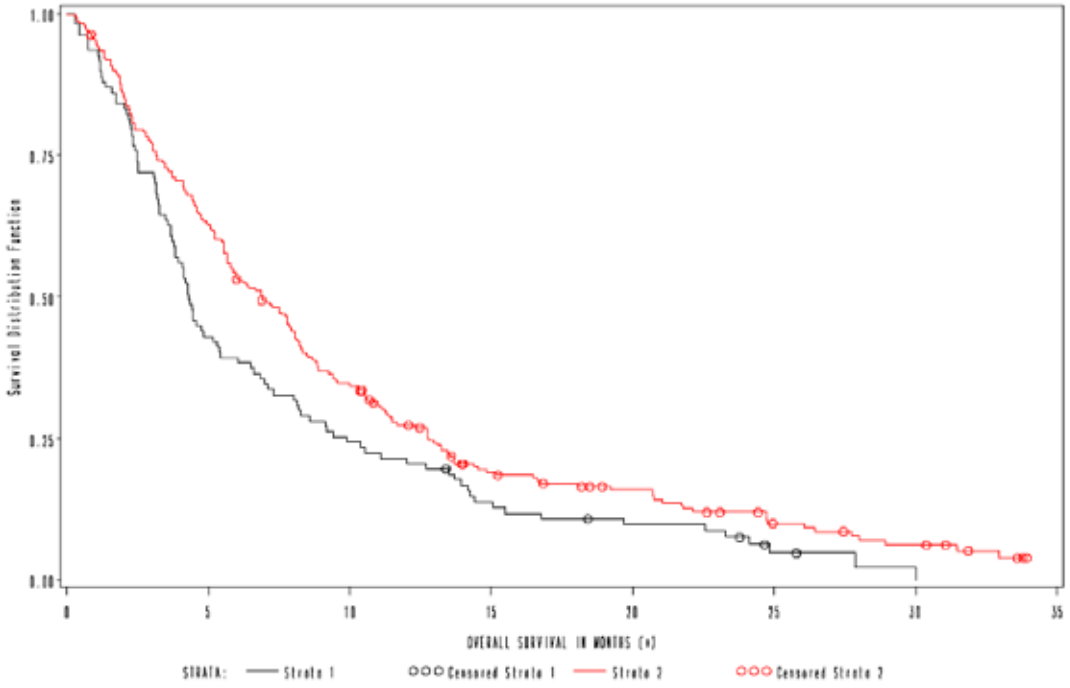
Median OS for the per protocol analysis was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm. The risk of death is reduced by 25% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.75 (95% CI: 0.59; 0.96 p=0.0197) In a subsequent update, OS in the per protocol patient population showed a 2 month 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) (see Table 22 and Figure 4.). This difference was statistically significant (p = 0.0130).

Table 22: Overall survival: Per-protocol patients (Cut-off 31May 2007)

	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	

a: Log-rank test stratified

Figure 4: Overall survival: Per-protocol patients (Cut-off May 31st 2007)



Overall Survival - Eligible patients

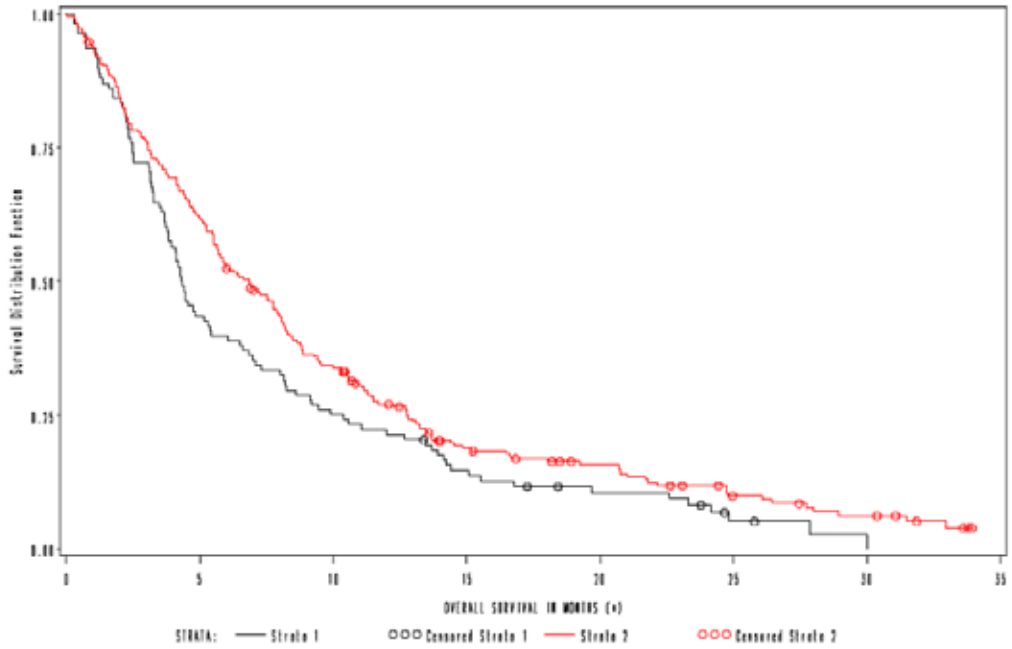
Table 23 below shows the updated overall survival in eligible patients (357 patients). These data confirmed earlier results, showing a median two-month advantage in survival favouring VFL+BSC. The risk of death was reduced by 23 %, HR: 0.77 (95% CI: 0.61, 0.98) and this difference is statistically significant (p= 0.032) (Table 23 and Figure 5).

Table 23: Overall survival: Eligible patients (cut-off 31 May 2007)

	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	

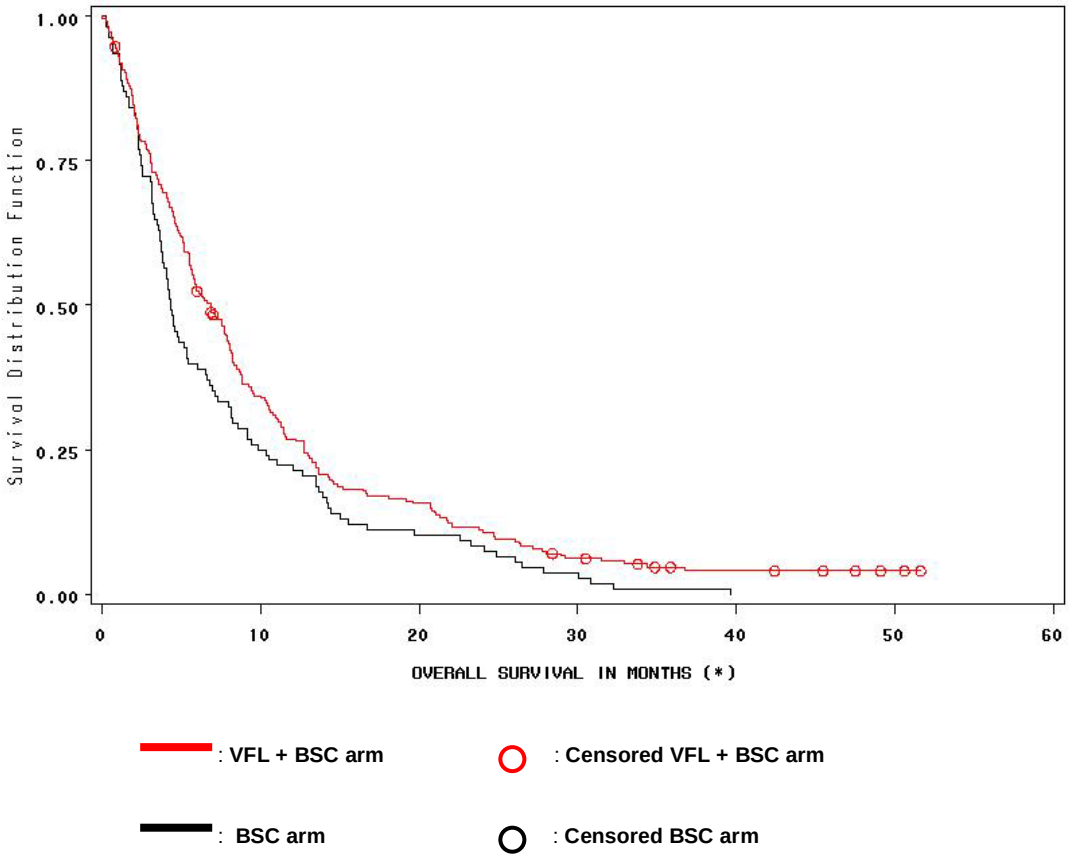
a: Log-rank test stratified

Figure 5: Overall survival: Eligible patients (cut-off 31 May 2007)



Overall survival data were further updated on 30 November 2008, and results still confirmed the previous reported data of two 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 is statistically significant (p=0.0227) (see Figure 6).

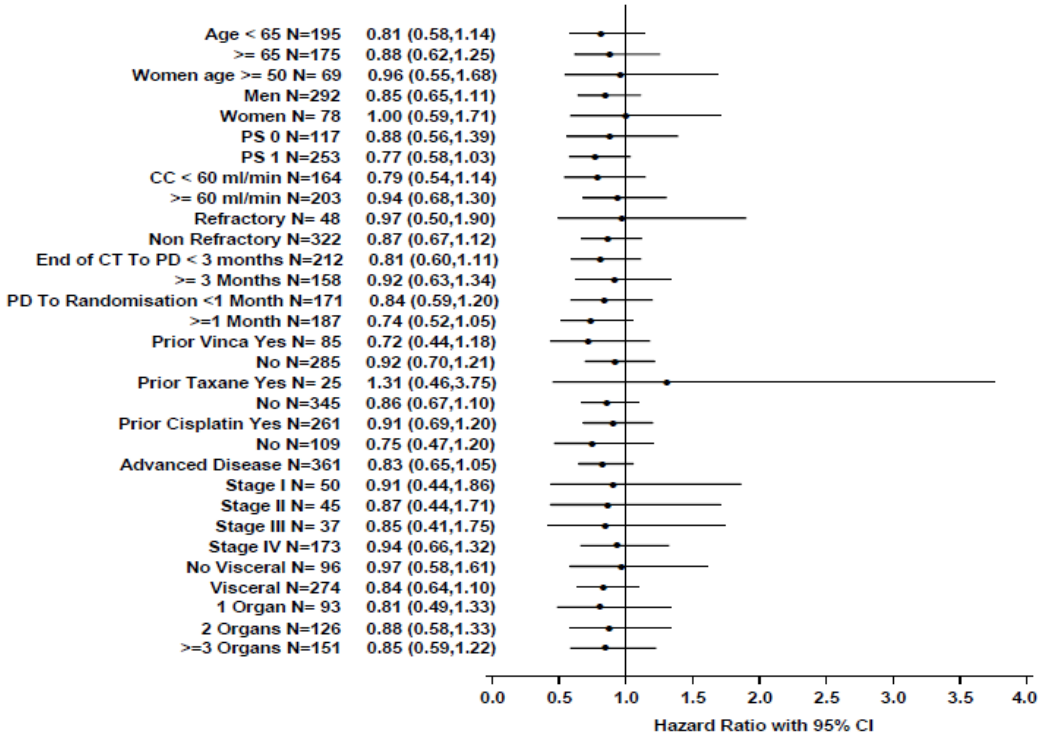
Figure 6: Overall survival: Eligible population (Cut-off: 30 November 2008)



Overall Survival by Subgroups

For the majority of subsets, overall survival was longer for the vinflunine arm compared with the BSCarm (HR < 0.95). See Figure 7 below.

Figure 7: Subset Analysis of Overall Survival by Groups

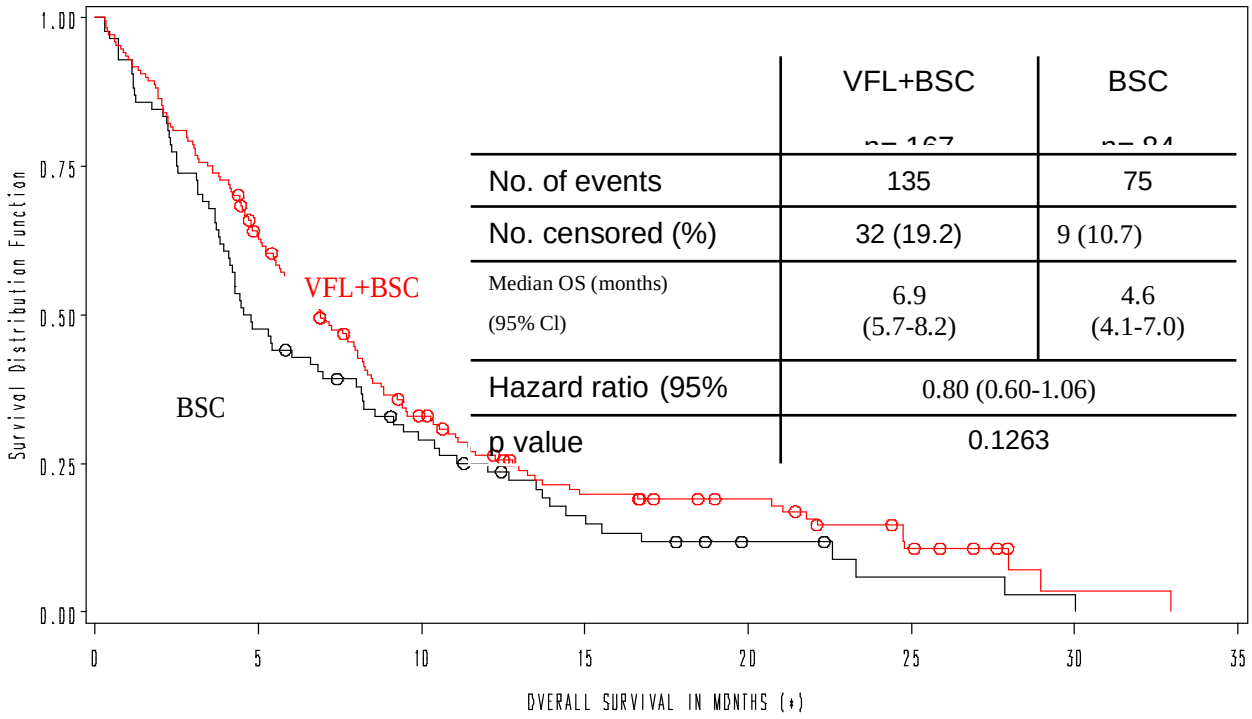


Stratified Cox proportional hazard model used for 95% CIs

Overall survival results according to prior platinum therapy in the eligible population are shown in Figure 8.

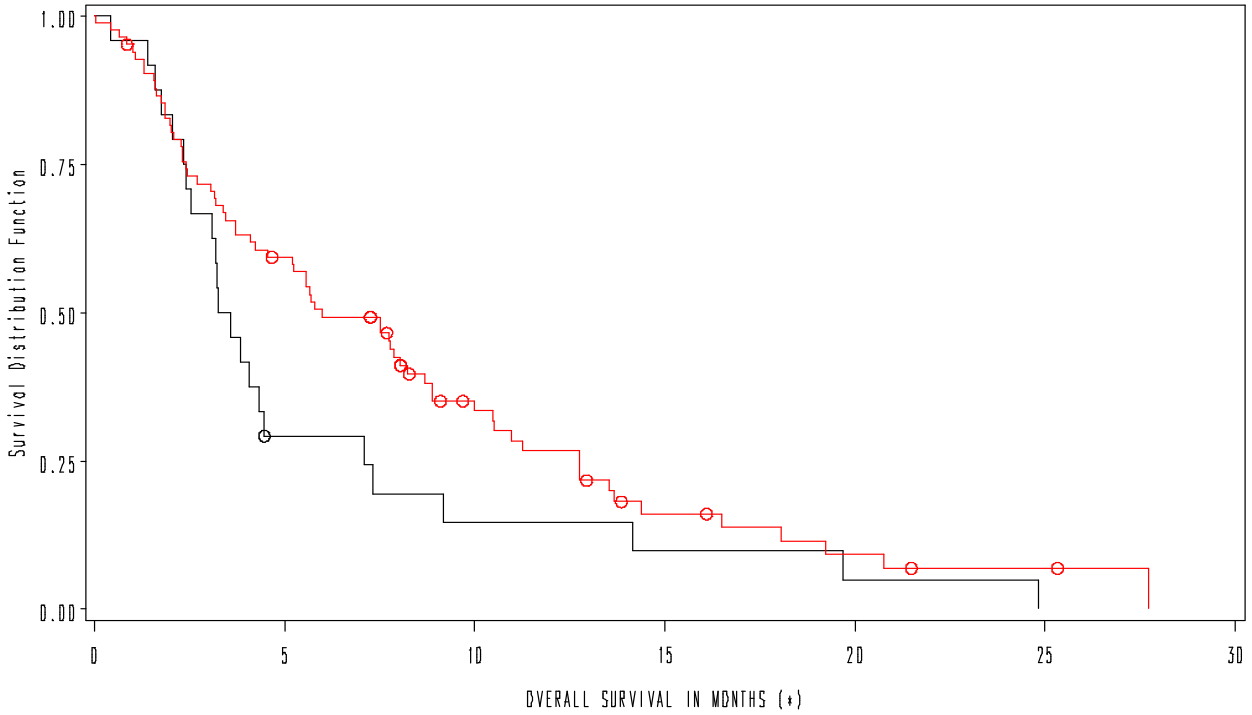
Overall survival in patients without prior cisplatin therapy is shown in Figure 9.

Figure 8: Kaplan-Meier Plot of Overall Survival in Patients with Prior Cisplatin Regimen - Eligible Population



	VFL+BSC	BSC
	n= 167	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%	0.80 (0.60-1.06)	
p value	0.1263	

Figure 9: Kaplan-Meier Plot of Overall Survival in Patients without Prior Cisplatin Regimen - Eligible Population



Secondary endpoints

Progression-free Survival

All randomised population

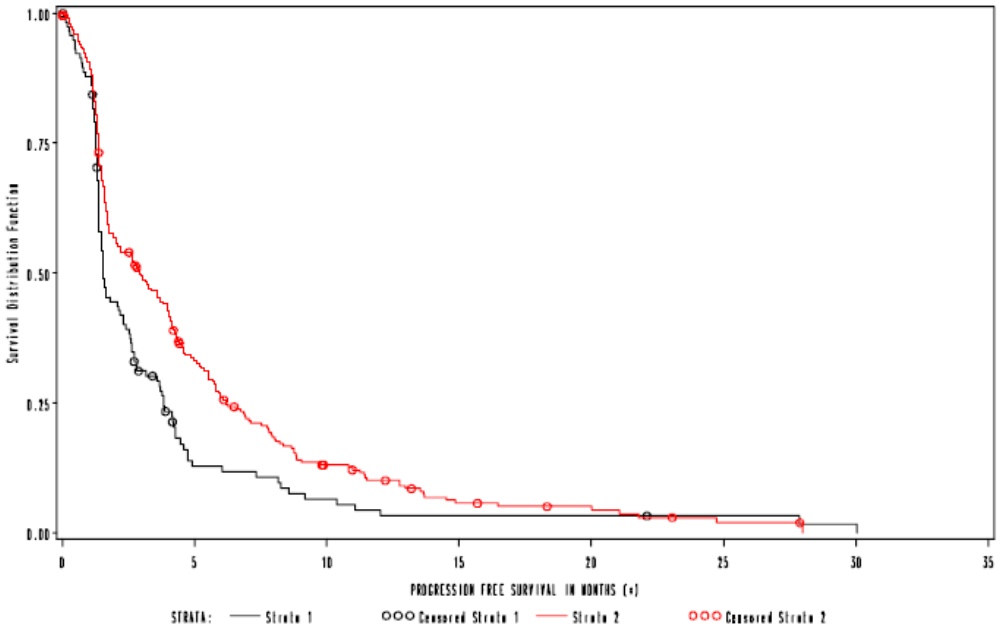
According to the IRC assessment (cut-off 31 May 2007), PFS was significantly longer for the VFL+BSC arm than for the BSC arm in the whole randomised population (3.0 months versus 1.5 months, $p < 0.01$) (see Table 24, Figure 10).

Table 24: IRC Assessed 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)
Median in months (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	

a: Log rank test stratified

Figure 10: IRC Assessed Progression Free Survival: All Randomised Patients



Evaluable population

According to the IRC assessment, PFS was significantly longer for the VFL+BSC group in the response evaluable population (3.1 months versus 1.4 months, $p < 0.0001$) (Table 25, Figures 11 and 12).

Table 25: IRC Assessed Progression-free Survival: Response Evaluable Patients

	VFL+BSC (N=185)	BSC (N=85)
No. of events	171	82
No. censored (%)	14 (7.6)	3 (3.5)
Median in months (95% CI)	3.1 (2.1, 4.0)	1.4 (1.4, 1.5)
Hazard ratio (95% CI)	0.52 (0.40, 0.69)	
p value[a]	< 0.0001	

a: Log-rank test stratified

Progression-Free Survival – Prior platinum therapy – Eligible Population

Figure 11: Kaplan-Meier Plot of Progression Free Survival in Patients with Prior Cisplatin Regimen - Eligible Population

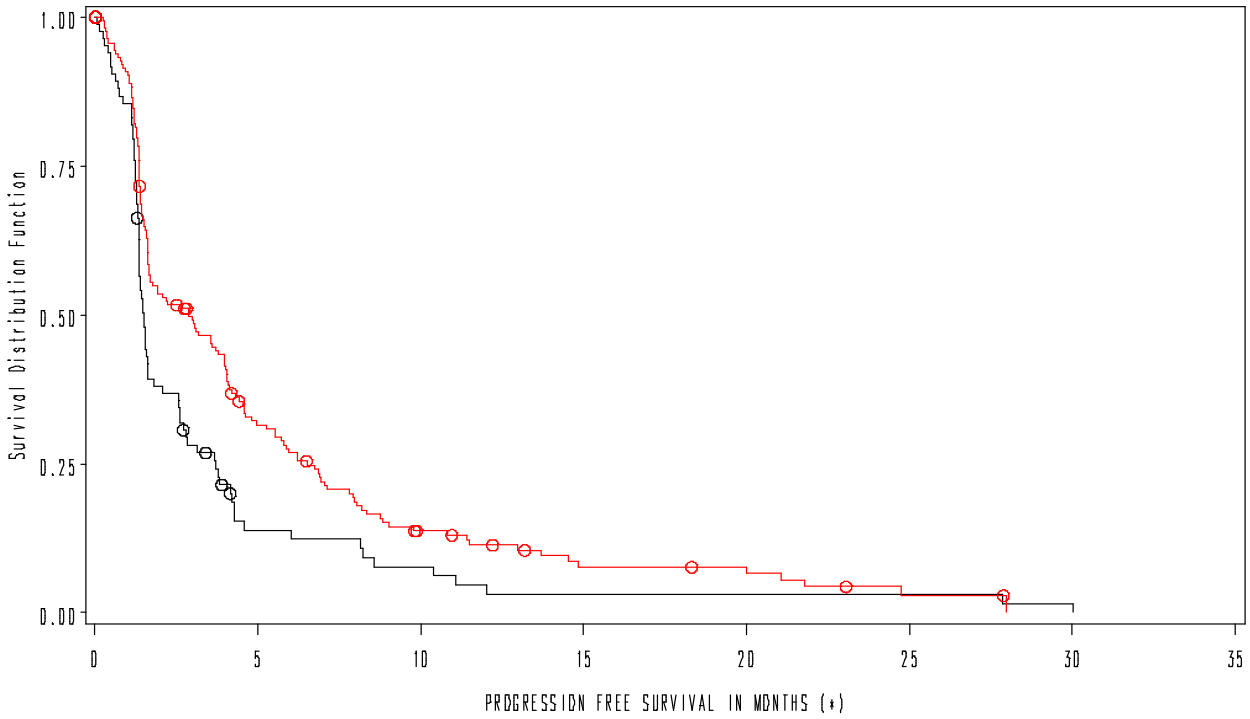
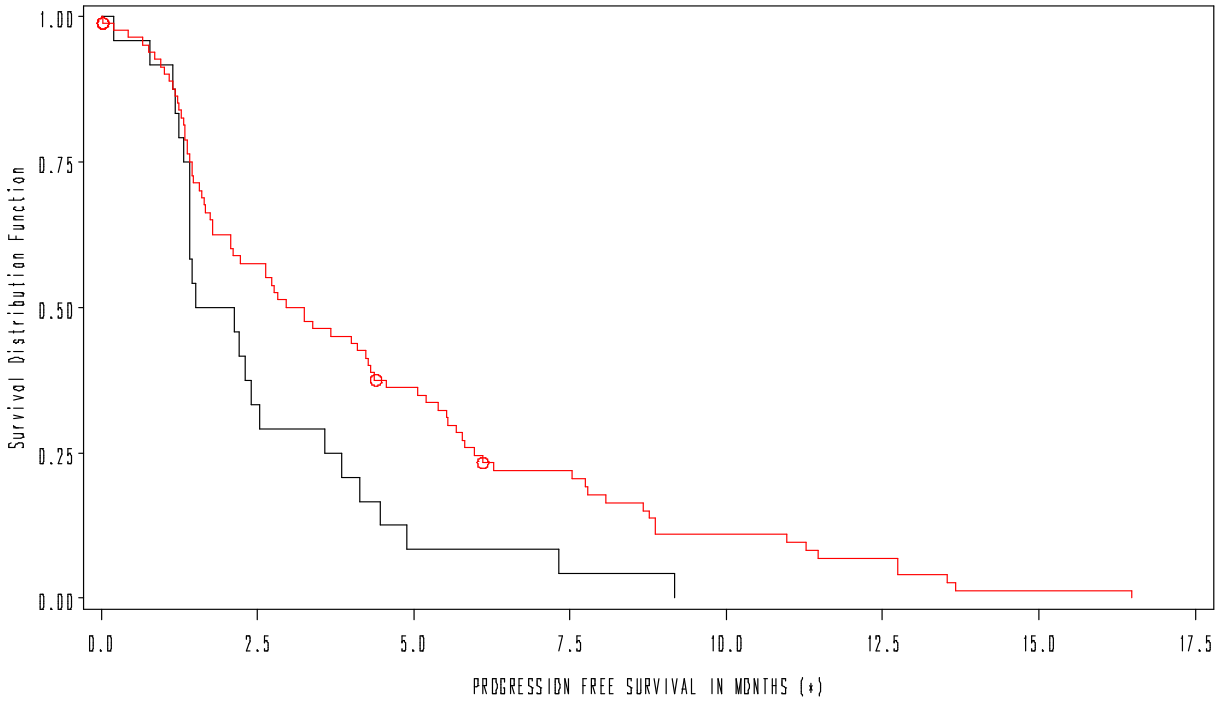


Figure 12: Kaplan-Meier Plot of Progression Free Survival in Patients without Prior Cisplatin Regimen - Eligible Population



Tumour Response rate

According to investigator assessment, 54% of randomised patients in the VFL+BSC group compared with 22% in the BSC group had a PR or SD as their best response. The objective tumour response rate in the VFL+BSC group was significantly higher compared with the BSC group in the randomised population (11.1% versus 0%, p=0.0002). Best response and objective response after IRP assessment is summarised in Table 26.

Table 26: Best Response and Objective Response After IRP Assessment: Response Evaluable VFL Patients

	Number of Patients (%)
	VFL+BSC (N=210)
Complete response (CR)	1 (0.5)
Partial response (PR)	24 (11.4)
Stable disease (SD)	105 (50.0)
Progressive disease (PD)	80 (38.1)
Objective response (CR+PR)	25
Objective response rate (95% CI)	11.9 (7.9, 17.1)

Investigator assessed best response is summarised in Table 27.

Table 27: Investigator Assessed Best Response: Response Evaluable Population (November 2006)

	Number (%) of Patients	
	VFL+BSC (N=215)	BSC (N=93)
Complete response	0	0
Partial response (PR)	28 (13.0)	0
Stable disease (SD)	106 (49.3)	21 (22.6)
Progressive disease (PD)	81 (37.7)	72 (77.4)

Results from the additional efficacy analyses in May 2007 are shown in Table 28 below.

Table 28: Best Response and Objective Response After IRC Assessment: Evaluable Patients

	Number of Patients (%)	
	VFL+BSC (N=185)	BSC (N=85)
Complete response (CR)	0	0
Partial response (PR)	16 (8.6)	0
Stable disease (SD)	86 (46.5)	23 (27.1)
Progressive disease (PD)	83 (44.9)	62 (72.9)
Objective response (CR+PR)	16	0
Objective response rate (95% CI)	8.6 (5.0, 13.7)	-

Disease Control Rate

All randomised population

According to IRC assessment, the disease control rate, in randomised patients, was significantly higher in the VFL+BSC arm (41.1% versus 24.8%, p = 0.0024) (see Table 29)

Table 29: IRC Assessed Disease Control Rate: All Randomised Patients

	VFL+BSC (N=253)	BSC (N=117)
No. of patients with disease control (CR+PR+SD)	104	29
Disease control rate (95% CI)[a]	41.1% (35.0, 47.4)	24.8% (17.3, 33.6)
p value[b]	0.0024	

a: 95% exact binomial CI
b: Cochran-Mantel-Haenszel test (this test was stratified by refractory status only because too many centers had to be opened to complete the study)

Evaluable population

According to IRC assessment, the disease control rate in response evaluable patients, was significantly higher in the VFL+BSC arm (55.1% versus 27.1%, p<0.0001) (Table 30).

Table 30: IRC Assessed Disease Control Rate: Response Evaluable Patients

	VFL+BSC (N=185)	BSC (N=85)
No. of patients with disease control (CR+PR+SD)	102	23
Disease control rate (95% CI)[a]	55.1% (47.7, 62.4)	27.1% (18.0, 37.8)
p value[b]	< 0.0001	

a: 95% exact binomial CI
b: Cochran-Mantel-Haenszel test (this test was stratified by refractory status only because too many centres had to be opened to complete the study)

Duration of Disease Control

According to IRC assessment, the median duration of disease control in the randomised population was longer in the VFL+BSC arm than in the BSC arm (5.7 months versus 4.2 months) (Table 31). Results for the IRC assessed median duration of disease control in the response evaluable population were similar to those of the randomised population.

Table 31: IRC Assessed Duration of Disease Control: Randomised Patients with at least Stable Disease

	VFL+BSC (N=253)	BSC (N=117)
Number with disease control (CR+PR+SD)	104	29
Median in months (95% CI)[a]	5.7 (5.0, 6.3)	4.2 (3.8, 4.9)

a: Kaplan-Meier method

Other Assessments

Quality of Life

VFL+BSC did not produce a decrease in HRQL when compared to BSC alone. 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, repeated measure analysis). There was a decrement in the global health status score for both groups until Week 6. By Week 18 there was a positive change in the global health status score. For the BSC arm, there was a continuous decrement in change from baseline through Week 18. There was no collection of quality of life assessment after Week 18.

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-Melzack 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 two treatment arms for WHO PS ≥ 1 (71.5% and 61.5% for the vinflunine + BSC and BSC arms, respectively). 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 SAP (treatment group, alkaline phosphatase, haemoglobin, visceral metastases, ECOG PS, 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 alone, with a Hazard Ratio HR of 0.77 (95% CI: 0.61 - 0.98, p = 0.0360) (see Table 32 below).

Table 32: 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).
b: Wald Chi square test

An additional multivariate analysis of overall survival using a Cox proportional hazard model was also conducted in the eligible (modified intention –to-treat (ITT)) population and showed a statistically significant effect of the treatment arm on survival (p=0.0027) (see Table 33 below).

Table 33: 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, ³ median), haemoglobin (< median, ³ median), visceral metastases (yes, no), WHO PS (0, ³ 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 PS showed evidence of deviation from the proportional hazards

assumption (p=0.028). Thus, the Cox model, stratified by PS, was used. The results are given in Table 34 below.

Table 34: 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
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, ³ median), haemoglobin (< median, ³ median), visceral metastases (yes, no), Refractory status (Refractory, non refractory), radiotherapy of the pelvis (yes, no).
b: Wald Chi square test

When the proportional hazards assumption was tested in the model stratified on the PS, 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) was apparent according to the multivariate Cox analysis (Table 35) leading to the conclusion that the multivariate model that should be analysed in the eligible population is the one without the cisplatin covariate. In this analysis (Table 36), it was found that VFL significantly improves the Overall Survival of the patients (HR: 0.686 (0.536, 0.877; p-value: 0. 0027).

Table 35: 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

Table 36: 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

Variables at Randomisation	Hazard Ratio (95% CI)	p Value
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

There was no apparent effect of prior cisplatin (p=0.8039) and no interaction between treatment group and prior cisplatin (p=0.9716) (see Table 37 below). 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 analysing the PFS. In this model, the effect of the treatment group is found to be significant (p=0.0001).

Table 37: 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

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 the creatinine clearance (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

An open-label, Phase I, pharmacokinetic dose adjustment study of IV vinflunine in cancer patients with liver dysfunction was conducted during the drug development (CSR L0070 IN 104). 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 three 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 biological variables at baseline (bilirubin, SGOT, SGPT, ALP, GGT, total plasma protein and prothrombin 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. 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. Results are not yet available.

Analysis performed across trials (pooled analyses and meta-analyses)

No pooled or meta-analyses were performed.

Supportive studies

Study VFL 202

Study design

This was an open-label, multicentre (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.

It was designed to determine the efficacy of vinflunine in patients with advanced TCCU previously treated with one platinum-based line of chemotherapy. The one-sample multiple testing procedure of Fleming for Phase II clinical trials was used. A minimum of 25 evaluable patients and a maximum of 50 evaluable patients were required, depending on the response rate observed in the first 25 subjects. A small excess in recruitment was allowed to replace possible drop-outs due to protocol non-compliance.

Six patients were treated at the beginning of study with IV vinflunine at 350 mg/m² every 3 weeks. Subsequently patients received a reduced dose of 320 mg/m² every 3 weeks. The initial treatment dose and schedule of 350 mg/m^2 every 3 weeks was based on the recommended dose schedule established in a previous vinflunine Phase I study (Pierre Fabre Medicament 2002). A preliminary safety evaluation, performed on the first 25 patients included in all vinflunine Phase II trials (among these the 6 patients included in this trial) led to a reduction in vinflunine dose to 320 mg/m² every 3 weeks for all subsequent patients.

Treatment was to be modified on the basis of haematological and/or non-haematological toxicities. Dose adjustments and/or delays were to be made according to the body system showing the greatest degree of toxicity. Patients were to be treated until documented disease progression, unacceptable toxicity or patient refusal.

Efficacy was assessed in all patients included in the study who received at least one cycle of vinflunine using intent-to-treat rules. Also, a per protocol analysis was performed on eligible and evaluable patients. Efficacy was assessed using the WHO criteria.

Objectives

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 two consecutive assessments. Tumour assessment was performed every two cycles.

Study population

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 performance status based on the Karnofsky score (KPS)[18] > 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%). Some 51% of patients had progressed within 6 months of their prior chemotherapy.

Study treatments

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.

Efficacy Results

Valid conclusions could only be drawn from the 51 patients who were treated at 320 mg/m².

In the first step of the Fleming's procedure, which required 25 evaluable patients, 5 patients responded to the treatment achieving a response rate of 20%. The number of responding patients permitted rejection of the H0 hypothesis and the investigation of vinflunine in a Phase III trial was warranted. In order to confirm this observation and to reduce the 95% confidence interval, 25 additional patients were included. After external review an objective response rate of 18% [95% CI: 8.4-30.9%] was achieved in ITT patients and 17% [95% CI: 7.7-30.8%] in evaluable patients. A total of 67% and 70% of patients achieved disease control in the ITT and evaluable patient populations, respectively.

Considering the time elapsed between the end of the treatment with platinum-containing regimens and inclusion in the study, three groups can be identified: those patients who relapsed at less than 3 months (37.3%) who may be considered as refractory patients (poor prognosis), patients relapsing between 3 to 12 months after platinum (47.1%), and patients having relapsed after > 12 months (15.7%). The latter two subgroups were considered as non-

[18] Performance status is an attempt to quantify cancer patients' general well-being. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary, and as a measure for the required intensity of palliative care. It is also used in oncological randomized controlled trials as a measure of quality of life. The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death. Although the score has been described with intervals of 10, a practitioner may choose decimals if he or she feels a patient's situation holds somewhere between two marks.

refractory. A response rate of 10.5% (2 out of 19 patients) was achieved for the first group with a disease control (OR + NC) of 57.9%. The response rate observed in the second group was 25.0% (6 out of 24 patients) for a disease control of 70.8%. One out of 8 (12.5%) patients achieved a partial response in the third group, with a disease control of 75.0%. However because of the small number of patients in this last group, the results should be interpreted with caution. Other important facts are that three out of 9 responders were previously treated with a vinca-alkaloid containing regimen and five responding patients had visceral involvement.

The median duration of response was 9.1 months with a 95% confidence interval ranging from 4.2 to 15.0 months. The median progression-free survival calculated over the population treated at 320 mg/m² 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].

Study CA 001

Study design

This was an open-label, multicentre (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 27 January 2005 and the 10 April 2007.

Objectives

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), overall survival (OS) and evaluation of the safety profile of vinflunine and the vinflunine pharmacokinetic profile.

Study population

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).

Study treatments

Vinflunine was initially administered every 21 days; 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.

Efficacy Results

In the All-Treated population the primary endpoint of independently assessed response rate was 14.6% with a 95% CI of 9.4% to 21.2%. Many tumour responses were of long duration with a median of 6.0 months. The response rates in various patient subgroups, including those with visceral disease and renal impairment were similar to those in the overall population. Results are summarised in Table 38 below.

Table 38: Overall Summary of Efficacy

IRRC Best Response: All Treated Patients, N = 151	
Partial response, n (%)	22 (14.6)
Stable disease, n (%)	64 (42.4)
Progressive disease, n (%)	49 (32.5)
Not evaluable, n (%)	16 (10.6)
Response Rate % (95% CI) [a,b]	14.6% (9.4%, 21.2%)
Investigator Best Response: All Treated Patients, N = 151	
Complete respnse, n (%)	2 (1.3)
Partial response, n (%)	13 (8.6)
Stable disease, n (%)	68 (45.0)
Progressive disease, n (%)	49 (32.5)
Not evaluable, n (%)	19 (12.6)
Response Rate % (95% CI) [a,]	9.9% (5.7%, 15.9%)
Duration of Response (IRRC), N = 22	
Median (95% CI), months [c]	5.95 (5.42, 9.46)
Progression Free Survival (IRRC), N = 151; 28 patients censored	
Median (95% CI), months [c]	2.76 (2.56, 3.84)
Overall Survival (IRRC), N = 151; 65 patients censored	
Median (95% CI), months [c]	7.89 (6.67, 9.69)

[a] Number of responders (CR or PR) / Number of treated patients
[b] Two sided confidence interval (CI) calculated using the Clopper-Pearson method
[c] Two sided CI computed using the Brookmeyer Crowley method

Clinical evaluator's overall conclusions on clinical efficacy

The studies conducted to examine efficacy were appropriately designed and relevant clinical outcome measures were used. Methodologies used were also appropriate.

The primary analysis from the pivotal Study 302 case study report (CSR) failed to show a statistical significant difference in overall survival for vinflunine when compared to BSC in the ITT population. A difference in overall survival was only observed in secondary analyses, excluding patients from the ITT population. The primary analysis performed in the ITT population was affected by the higher proportion of noneligible patients in the BSC arm (9 non eligible patients for BSC versus 4 for VFL + BSC).

A significant treatment effect of vinflunine (p=0.036) on overall survival in the prespecified 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) supports the consistency of the results.

At the request of the European Medicines Agency (EMA) during the evaluation process, the sponsor submitted repeated analyses stratifying for Performance Status and thereby not relying on proportional hazards for this covariate. The results were consistent with those previously observed for the ITT population (p=0.0420, HR 0.776; 0.61, 0.99) and the eligible population (p=0.0067, HR=0.708; 0.55, 0.91).

EMA also requested presentation of efficacy results in relation to prior platinum based therapy. Based on these analyses, 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. The effect of the treatment arm was still found to be significant when adjusted for prior platinum based therapies.

The median overall survival was 6.9 months (vinflunine + BSC) versus 4.6 months (BSC). This 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 for the vinflunine + BSC arm which can be compared to 1.5 months for the BSC arm) (p=0.0012).

In the pre-specified multivariate analysis performed on the ITT population it was 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 in 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). These results are important because the population analysed 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 HRs (95% CI) of 0.53 (0.32 – 0.88; p=0.0143) and 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 HRs (95% CI) of 0.51(0.31 – 0.86; p=0.0111) and 0.63(0.48 – 0.84; p=0.0016), respectively.

In summary, results for the efficacy endpoint of overall survival showed a significant difference between the two treatment groups which favoured vinflunine. This result was supported 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 and supported 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 (30 November 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. However, there was still evidence of efficacy in the group of patients who had received prior cisplatin therapy.

The clinical evaluator was of the opinion that the efficacy results support effectiveness of vinflunine treatment in this patient group with a limited life expectancy and with an unmet medical need. The magnitude of the efficacy effects observed with vinflunine is considered clinically meaningful.

Safety

Introduction

The assessment of safety is based on data that were prepared by merging data bases from clinical trials using vinflunine in TCCU. Data from other clinical trials not involving TCCU patients were also presented.

Patient exposure

A total of 1203 patients have received 4617 cycles of vinflunine (VFL) as a single agent either in the TCCU indication or in Non-TCCU settings. Four hundred and fifty (450) patients with TCCU received VFL as a single agent. Of these 450 patients included in the 2 Phase II and the Phase III studies, 272 patients received the recommended dosage regimen of 320 mg/m² VFL every 3 weeks at least one time at Cycle 1 or 2, and 178 patients received an initial dosage regimen of 280 mg/m² every 3 weeks. Safety analyses included all subjects who received at least one dose of study medication.

In TCCU patients, 1202 and 620 cycles were administered in the 320 mg/m² and 280 mg/m² groups every 3 weeks, respectively. Regarding the total population treated (1203 patients), VFL was administered at 320 mg/m² and 280 mg/m² over 3997 and 620 cycles, respectively.

The median number of cycles delivered in the 320 mg/m² and 280 mg/m² groups of TCCU patients was 4 (range 1-21) and 2 (range 1-20) respectively. The median number of cycles administered was the same (3) in the TCCU and Non TCCU populations. In TCCU patients, it is noteworthy that the number of patients and the median number of cycles at 320 mg/m² every 3 weeks were higher than at 280 mg/m².

Median cumulative dose and median relative dose intensity (RDI) of vinflunine by patient are displayed in Table 39 below.

Table 39: Vinflunine cumulative dose, dose intensity and relative dose intensity per patient and according to data sets

	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

Tables 3-1, 3-7, 3-11, * patient 301 – 520364 had a dose interruption-By convention 0.01

Adverse events

The tables below present the AEs which were assessed by the investigators as study treatment related. The tables summarise the study treatment related "adverse events of special interest" by patient (TCCU and Non-TCCU patients) for all TCCU patients treated with vinflunine (Table 40) and for those treated with the 320 mg/m^2 dose (Table 41).

Table 40: Incidence in term of patients of study treatment-related adverse events by system organ class and preferred term whatever the dose – VFL TCCU (UTC) versus VFL all

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Diplopia			1(0.1%)		1(0.1%)	
- Dry eye	1(0.2%)				1(0.1%)	
- Eye pain			1(0.1%)		1(0.1%)	
- Eyelid ptosis			1(0.1%)		1(0.1%)	
- Eyelids pruritus			1(0.1%)		1(0.1%)	
- Keratoconjunctivitis sicca			1(0.1%)		1(0.1%)	
- Lacrimation increased			4(0.5%)		4(0.3%)	
- Ocular discomfort			1(0.1%)		1(0.1%)	
- Photopsia			1(0.1%)		1(0.1%)	
- Retinal vein thrombosis	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
- Vision blurred	1(0.2%)		16(2.1%)	1(0.1%)	17(1.4%)	1(0.1%)
- Visual acuity reduced	1(0.2%)				1(0.1%)	
- Visual disturbance			1(0.1%)		1(0.1%)	
- Vitreous floaters	1(0.2%)				1(0.1%)	
Gastrointestinal disorders	363(80.7%)	111(24.7%)	591(78.5%)	146(19.4%)	954(79.3%)	257(21.4%)
- Abdominal discomfort	3(0.7%)	1(0.2%)	2(0.3%)		5(0.4%)	1(0.1%)
- Abdominal distension	5(1.1%)		4(0.5%)	1(0.1%)	9(0.7%)	1(0.1%)
- Abdominal pain	76(16.9%)	18(4.0%)	200(26.6%)	44(5.8%)	276(22.9%)	62(5.2%)
- Abdominal pain lower	3(0.7%)		1(0.1%)		4(0.3%)	
- Abdominal pain upper	18(4.0%)	3(0.7%)	48(6.4%)	3(0.4%)	66(5.5%)	6(0.5%)
- Abdominal tenderness			2(0.3%)		2(0.2%)	
- Anal discomfort			1(0.1%)		1(0.1%)	
- Anal fistula			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Anal haemorrhage	1(0.2%)				1(0.1%)	
- Aptyalism			1(0.1%)		1(0.1%)	
- Cheilitis			1(0.1%)		1(0.1%)	
- Colonic pseudo-obstruction	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
- Constipation	247(54.9%)	69(15.3%)	405(53.8%)	76(10.0%)	652(54.2%)	144(12.0%)
- Diarrhoea	58(12.9%)	4(0.9%)	85(11.3%)	7(0.9%)	143(11.9%)	11(0.9%)

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
ANY ADVERSE EVENT	420(93.3%)	220(48.9%)	676(89.8%)	281(37.3%)	1096(91.1%)	501(41.6%)
Blood and lymphatic system disorders	33(7.3%)	32(7.1%)	34(4.5%)	33(4.4%)	67(5.6%)	65(5.4%)
- Disseminated intravascular coagulation	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
- Febrile neutropenia	30(6.7%)	30(6.7%)	34(4.5%)	33(4.4%)	64(5.3%)	63(5.2%)
- Pancytopenia	2(0.4%)	1(0.2%)			2(0.2%)	1(0.1%)
Cardiac disorders	14(3.1%)	6(1.3%)	15(2.0%)	3(0.4%)	29(2.4%)	9(0.7%)
- Arrhythmia supraventricular			1(0.1%)		1(0.1%)	
- Atrial fibrillation			1(0.1%)		1(0.1%)	
- Bradycardia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Cardiac failure			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Cardio-respiratory arrest	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
- Cardiogenic shock			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Myocardial infarction	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
- Myocardial ischaemia	3(0.7%)	3(0.7%)	2(0.3%)	1(0.1%)	5(0.4%)	4(0.3%)
- Palpitations	2(0.4%)		4(0.5%)		6(0.5%)	
- Sinus tachycardia	3(0.7%)	1(0.2%)	1(0.1%)		4(0.3%)	1(0.1%)
- Supraventricular extrasystoles	1(0.2%)				1(0.1%)	
- Tachycardia	3(0.7%)		4(0.5%)		7(0.6%)	
Ear and labyrinth disorders	14(3.1%)	2(0.4%)	31(4.1%)	2(0.3%)	45(3.7%)	4(0.3%)
- Deafness			1(0.1%)		1(0.1%)	
- Ear pain	6(1.3%)		12(1.6%)	1(0.1%)	18(1.5%)	1(0.1%)
- Tinnitus	4(0.9%)		6(0.8%)		10(0.8%)	
- Vertigo	3(0.7%)	2(0.4%)	14(1.9%)	1(0.1%)	17(1.4%)	3(0.2%)
- Vertigo positional	1(0.2%)				1(0.1%)	
Endocrine disorders			3(0.4%)	3(0.4%)	3(0.2%)	3(0.2%)
- Inappropriate antidiuretic hormone secretion			3(0.4%)	3(0.4%)	3(0.2%)	3(0.2%)
Eye disorders	5(1.1%)	1(0.2%)	28(3.7%)	1(0.1%)	33(2.7%)	2(0.2%)
- Blindness			1(0.1%)		1(0.1%)	
- Conjunctivitis			2(0.3%)		2(0.2%)	

Table 40 continued on next page.

Table 40 continued

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
Dry mouth	6(1.3%)		11(1.5%)		17(1.4%)	
Dyspepsia	25(5.6%)	1(0.2%)	32(4.2%)	1(0.1%)	57(4.7%)	2(0.2%)
Dysphagia	9(2.0%)	2(0.4%)	13(1.7%)	4(0.5%)	22(1.8%)	6(0.5%)
Epigastric discomfort	1(0.2%)		1(0.1%)		2(0.2%)	
Eructation	2(0.4%)		1(0.1%)		3(0.2%)	
Faecal incontinence	1(0.2%)				1(0.1%)	
Faeces discoloured	1(0.2%)				1(0.1%)	
Flatulence	9(2.0%)		21(2.8%)		30(2.5%)	
Gastric ulcer haemorrhage	1(0.2%)				1(0.1%)	
Gastritis	2(0.4%)		9(1.2%)	1(0.1%)	11(0.9%)	1(0.1%)
Gingival bleeding	1(0.2%)				1(0.1%)	
Gingival pain	2(0.4%)		1(0.1%)		3(0.2%)	
Glossodynia	2(0.4%)		4(0.5%)		6(0.5%)	
Haematemesis	2(0.4%)	1(0.2%)	1(0.1%)		3(0.2%)	1(0.1%)
Haemorrhoids	3(0.7%)				3(0.2%)	
Hypoaesthesia oral			2(0.3%)		2(0.2%)	
Ileus	11(2.4%)	10(2.2%)	14(1.9%)	10(1.3%)	25(2.1%)	20(1.7%)
Ileus paralytic	2(0.4%)	2(0.4%)			2(0.2%)	2(0.2%)
Intestinal obstruction	1(0.2%)				1(0.1%)	
Intestinal spasm			1(0.1%)		1(0.1%)	
Lip blister			1(0.1%)		1(0.1%)	
Lip dry	1(0.2%)				1(0.1%)	
Lip swelling			1(0.1%)		1(0.1%)	
Melaena	2(0.4%)	1(0.2%)			2(0.2%)	1(0.1%)
Mouth ulceration	1(0.2%)		1(0.1%)		2(0.2%)	
Nausea	184(40.9%)	13(2.9%)	323(42.9%)	22(2.9%)	507(42.1%)	35(2.9%)
Odynophagia	2(0.4%)	1(0.2%)	3(0.4%)		5(0.4%)	1(0.1%)
Oesophagitis	2(0.4%)	1(0.2%)	1(0.1%)		3(0.2%)	1(0.1%)
Oral discomfort	1(0.2%)				1(0.1%)	
Oral mucosal disorder	1(0.2%)				1(0.1%)	
Oral pain	6(1.3%)	1(0.2%)	10(1.3%)	2(0.3%)	16(1.3%)	3(0.2%)
Pancreatitis	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Paraesthesia oral	3(0.7%)		3(0.4%)		6(0.5%)	
Proctalgia	1(0.2%)				1(0.1%)	
Retching	2(0.4%)				2(0.2%)	
Saliva altered	1(0.2%)				1(0.1%)	
Salivary gland disorder			1(0.1%)		1(0.1%)	
Salivary hypersecretion			2(0.3%)		2(0.2%)	
Small intestinal obstruction	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Stomatitis	121(26.9%)	12(2.7%)	267(35.5%)	13(1.7%)	388(32.3%)	25(2.1%)
Subileus	1(0.2%)				1(0.1%)	
Swollen tongue	3(0.7%)		3(0.4%)		6(0.5%)	
Tongue blistering	1(0.2%)				1(0.1%)	
Tongue disorder			1(0.1%)		1(0.1%)	
Tongue ulceration			3(0.4%)		3(0.2%)	
Toothache	1(0.2%)		1(0.1%)		2(0.2%)	
Vomiting	123(27.3%)	13(2.9%)	233(30.9%)	22(2.9%)	356(29.6%)	35(2.9%)
General disorders and administration site conditions	325(72.2%)	80(17.8%)	511(67.9%)	100(14.3%)	836(69.5%)	180(15.4%)
Asthenia	20(4.4%)	5(1.1%)	5(0.7%)	2(0.3%)	25(2.1%)	7(0.6%)
Catheter site rash			1(0.1%)		1(0.1%)	
Chest discomfort			2(0.3%)		2(0.2%)	
Chest pain	15(3.3%)	3(0.7%)	39(5.2%)	9(1.2%)	54(4.5%)	12(1.0%)
Chills	10(2.2%)	1(0.2%)	17(2.3%)		27(2.2%)	1(0.1%)
Condition aggravated	1(0.2%)	1(0.2%)	4(0.5%)	2(0.3%)	5(0.4%)	3(0.2%)
Early satiety	1(0.2%)				1(0.1%)	
Extravasation	3(0.7%)		2(0.3%)		5(0.4%)	
Facial pain	1(0.2%)				1(0.1%)	
Fatigue	233(51.8%)	66(14.7%)	414(55.0%)	89(11.8%)	647(53.8%)	155(12.9%)

Table 40 continued

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
Inflammation	1(0.2%)				1(0.1%)	
Influenza like illness	3(0.7%)		3(0.4%)		6(0.5%)	
Infusion related reaction	5(1.1%)				5(0.4%)	
Infusion site erythema	1(0.2%)		8(1.1%)		9(0.7%)	
Infusion site pain	10(2.2%)		25(3.3%)	1(0.1%)	35(2.9%)	1(0.1%)
Infusion site phlebitis	1(0.2%)		4(0.5%)		5(0.4%)	
Infusion site reaction	5(1.1%)		49(6.5%)		54(4.5%)	
Infusion site swelling			1(0.1%)		1(0.1%)	
Injection site anaesthesia			1(0.1%)		1(0.1%)	
Injection site erythema	6(1.3%)		3(0.4%)		9(0.7%)	
Injection site hypersensitivity	1(0.2%)				1(0.1%)	
Injection site irritation	6(1.3%)		1(0.1%)		7(0.6%)	
Injection site pain	20(4.4%)		5(0.7%)		25(2.1%)	
Injection site phlebitis	11(2.4%)		4(0.5%)		15(1.2%)	
Injection site pruritus	3(0.7%)		1(0.1%)		4(0.3%)	
Injection site rash	2(0.4%)				2(0.2%)	
Injection site reaction	78(17.3%)	2(0.4%)	88(11.7%)	2(0.3%)	166(13.8%)	4(0.3%)
Injection site swelling			1(0.1%)		1(0.1%)	
Injection site urticaria	2(0.4%)		1(0.1%)		3(0.2%)	
Injection site vesicles			1(0.1%)		1(0.1%)	
Local swelling			1(0.1%)		1(0.1%)	
Malaise	2(0.4%)		1(0.1%)		3(0.2%)	
Mucosal inflammation			1(0.1%)		1(0.1%)	
Non-cardiac chest pain	1(0.2%)				1(0.1%)	
Oedema	1(0.2%)		3(0.4%)		4(0.3%)	
Oedema peripheral	5(1.1%)		2(0.3%)		7(0.6%)	
Pain	16(3.6%)	1(0.2%)	13(1.7%)	7(0.9%)	29(2.4%)	8(0.7%)
Peripheral coldness	1(0.2%)		1(0.1%)		2(0.2%)	
Pyrexia	49(10.9%)	2(0.4%)	71(9.4%)	6(0.8%)	120(10.0%)	8(0.7%)
Hepatobiliary disorders	1(0.2%)		1(0.1%)		2(0.2%)	
Hepatic pain	1(0.2%)		1(0.1%)		2(0.2%)	
Immune system disorders	9(2.0%)	1(0.2%)	12(1.6%)	2(0.3%)	21(1.7%)	3(0.2%)
Hypersensitivity	8(1.8%)	1(0.2%)	12(1.6%)	2(0.3%)	20(1.7%)	3(0.2%)
Seasonal allergy	1(0.2%)				1(0.1%)	
Infections and infestations	45(10.0%)	30(6.7%)	70(9.3%)	35(4.6%)	115(9.6%)	65(5.4%)
Abscess	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Bacteraemia	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Bronchitis	2(0.4%)		4(0.5%)	1(0.1%)	6(0.5%)	1(0.1%)
Bronchitis acute			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Candidiasis	4(0.9%)				4(0.3%)	
Catheter related infection	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Cellulitis			2(0.3%)	2(0.3%)	2(0.2%)	2(0.2%)
Cystitis	1(0.2%)		1(0.1%)		2(0.2%)	
Ear infection			1(0.1%)		1(0.1%)	
Escherichia sepsis	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Herpes simplex			5(0.7%)	1(0.1%)	5(0.4%)	1(0.1%)
Herpes virus infection	1(0.2%)				1(0.1%)	
Hordeolum			1(0.1%)		1(0.1%)	
Infection	2(0.4%)	1(0.2%)	5(0.7%)	3(0.4%)	7(0.6%)	4(0.3%)
Influenza			1(0.1%)		1(0.1%)	
Injection site infection			1(0.1%)		1(0.1%)	
Laryngopharyngitis			1(0.1%)		1(0.1%)	
Lobar pneumonia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Lower respiratory tract infection			2(0.3%)	1(0.1%)	2(0.2%)	1(0.1%)
Lung infection			2(0.3%)	2(0.3%)	2(0.2%)	2(0.2%)
Nasopharyngitis	1(0.2%)		1(0.1%)		2(0.2%)	
Neutropenic infection	17(3.8%)	17(3.8%)	8(1.1%)	8(1.1%)	25(2.1%)	25(2.1%)
Neutropenic sepsis	1(0.2%)	1(0.2%)	3(0.4%)	3(0.4%)	4(0.3%)	4(0.3%)
Oral candidiasis	2(0.4%)		4(0.5%)		6(0.5%)	
Oral infection	2(0.4%)	1(0.2%)	2(0.3%)	1(0.1%)	4(0.3%)	2(0.2%)
Pharyngitis			6(0.8%)	1(0.1%)	6(0.5%)	1(0.1%)
Pneumonia	5(1.1%)	5(1.1%)	3(0.4%)	1(0.1%)	8(0.7%)	6(0.5%)
Pyelonephritis	1(0.2%)				1(0.1%)	
Rhinitis			1(0.1%)		1(0.1%)	
Sepsis	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Septic shock	1(0.2%)	1(0.2%)	3(0.4%)	3(0.4%)	4(0.3%)	4(0.3%)
Tonsillitis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Tooth infection			1(0.1%)		1(0.1%)	
Upper respiratory tract infection	2(0.4%)		4(0.5%)		6(0.5%)	
Urinary tract infection	7(1.6%)	2(0.4%)	6(0.8%)	4(0.5%)	13(1.1%)	6(0.5%)
Vaginal candidiasis			1(0.1%)		1(0.1%)	
Viral infection			1(0.1%)		1(0.1%)	
Wound infection	1(0.2%)		1(0.1%)		2(0.2%)	
Injury, poisoning and procedural complications	4(0.9%)	1(0.2%)	2(0.3%)		6(0.5%)	1(0.1%)
Collapse of lung			1(0.1%)		1(0.1%)	
Contusion			1(0.1%)		1(0.1%)	
Fall	3(0.7%)	1(0.2%)			3(0.2%)	1(0.1%)
Ureterostomy site discomfort	1(0.2%)				1(0.1%)	
Investigations	110(24.4%)	3(0.7%)	141(18.7%)	7(0.9%)	251(20.9%)	10(0.8%)
Alanine aminotransferase increased	2(0.4%)		1(0.1%)	1(0.1%)	3(0.2%)	1(0.1%)
Aspartate aminotransferase increased	1(0.2%)		1(0.1%)		2(0.2%)	
Electrocardiogram ST segment abnormal	1(0.2%)				1(0.1%)	
Electrocardiogram T wave abnormal			1(0.1%)		1(0.1%)	
Gamma-glutamyltransferase increased			4(0.5%)	3(0.4%)	4(0.3%)	3(0.2%)
Neutrophil count increased	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Troponin I increased			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Weight decreased	108(24.0%)	2(0.4%)	135(17.9%)	2(0.3%)	243(20.2%)	4(0.3%)

Table 40 continued

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Weight increased	1(0.2%)				1(0.1%)	
Metabolism and nutrition disorders	170(37.8%)	22(4.9%)	183(24.3%)	21(2.8%)	353(29.3%)	43(3.6%)
- Acidosis	1(0.2%)				1(0.1%)	
- Anorexia	155(34.4%)	12(2.7%)	176(23.4%)	14(1.9%)	331(27.5%)	26(2.2%)
- Dehydration	20(4.4%)	9(2.0%)	11(1.5%)	7(0.9%)	31(2.6%)	16(1.3%)
- Gout	1(0.2%)				1(0.1%)	
- Hyperglycaemia	3(0.7%)	3(0.7%)	2(0.3%)	2(0.3%)	5(0.4%)	5(0.4%)
- Hypoalbuminaemia	1(0.2%)				1(0.1%)	
- Hypoglycaemia	1(0.2%)	1(0.2%)	1(0.1%)		2(0.2%)	1(0.1%)
- Hypomagnesaemia	2(0.4%)				2(0.2%)	
- Hypovolaemia	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Musculoskeletal and connective tissue disorders	147(32.7%)	25(5.6%)	254(33.7%)	42(5.6%)	401(33.3%)	67(5.6%)
- Arthralgia	32(7.1%)	3(0.7%)	74(9.8%)	11(1.5%)	106(8.8%)	14(1.2%)
- Back pain	22(4.9%)	2(0.4%)	19(2.5%)	2(0.3%)	41(3.4%)	4(0.3%)
- Bone pain	11(2.4%)		19(2.5%)	6(0.8%)	30(2.5%)	6(0.5%)
- Flank pain	3(0.7%)		2(0.3%)	1(0.1%)	5(0.4%)	1(0.1%)
- Groin pain	2(0.4%)	1(0.2%)	1(0.1%)		3(0.2%)	1(0.1%)
- Joint stiffness	1(0.2%)				1(0.1%)	
- Muscle contracture	1(0.2%)				1(0.1%)	
- Muscle spasms	8(1.8%)		6(0.8%)		14(1.2%)	
- Muscular weakness	10(2.2%)	4(0.9%)	17(2.3%)	2(0.3%)	27(2.2%)	6(0.5%)
- Musculoskeletal chest pain	5(1.1%)	1(0.2%)	1(0.1%)		6(0.5%)	1(0.1%)
- Musculoskeletal discomfort			1(0.1%)		1(0.1%)	
- Musculoskeletal pain	9(2.0%)		4(0.5%)	1(0.1%)	13(1.1%)	1(0.1%)
- Musculoskeletal stiffness	1(0.2%)		1(0.1%)	1(0.1%)	2(0.2%)	1(0.1%)
- Myalgia	74(16.4%)	14(3.1%)	146(19.4%)	26(3.5%)	220(18.3%)	40(3.3%)
- Myositis			1(0.1%)		1(0.1%)	
- Neck pain	7(1.6%)		5(0.7%)		12(1.0%)	
- Pain in extremity	15(3.3%)		13(1.7%)	1(0.1%)	28(2.3%)	1(0.1%)
- Pain in jaw	15(3.3%)		50(6.6%)	6(0.8%)	65(5.4%)	6(0.5%)
- Polyarthritis			1(0.1%)		1(0.1%)	
- Trismus	1(0.2%)		1(0.1%)		2(0.2%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6(1.3%)	1(0.2%)	17(2.3%)	4(0.5%)	23(1.9%)	5(0.4%)
- Cancer pain	5(1.1%)	1(0.2%)	16(2.1%)	4(0.5%)	21(1.7%)	5(0.4%)
- Metastatic pain	1(0.2%)		2(0.3%)		3(0.2%)	
Nervous system disorders	118(26.2%)	17(3.8%)	210(27.9%)	17(2.3%)	328(27.3%)	34(2.8%)
- Ageusia	1(0.2%)				1(0.1%)	
- Akinaesthesia			1(0.1%)		1(0.1%)	
- Amnesia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Aphonia			2(0.3%)		2(0.2%)	
- Areflexia			3(0.4%)		3(0.2%)	
- Burning sensation			2(0.3%)		2(0.2%)	
- Convulsion	1(0.2%)	1(0.2%)	2(0.3%)	2(0.3%)	3(0.2%)	3(0.2%)
- Coordination abnormal			1(0.1%)		1(0.1%)	
- Depressed level of consciousness	1(0.2%)	1(0.2%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
- Disturbance in attention			2(0.3%)		2(0.2%)	
- Dizziness	24(5.3%)	2(0.4%)	27(3.6%)	2(0.3%)	51(4.2%)	4(0.3%)
- Dysaesthesia			1(0.1%)		1(0.1%)	
- Dysgeusia	13(2.9%)		24(3.2%)		37(3.1%)	
- Dysphasia			1(0.1%)		1(0.1%)	
- Extrapyramidal disorder			2(0.3%)	1(0.1%)	2(0.2%)	1(0.1%)
- Headache	28(6.2%)	3(0.7%)	65(8.6%)	4(0.5%)	93(7.7%)	7(0.6%)
- Hyperaesthesia	1(0.2%)				1(0.1%)	
- Hypersomnia	1(0.2%)				1(0.1%)	
- Hypoaesthesia	7(1.6%)		8(1.1%)		15(1.2%)	
- Lethargy	2(0.4%)		2(0.3%)		4(0.3%)	
- Neuralgia	27(6.0%)	2(0.4%)	34(4.5%)	4(0.5%)	61(5.1%)	6(0.5%)
- Neuropathy	5(1.1%)				5(0.4%)	

Neuropathy peripheral	4(0.9%)				4(0.3%)	
Paraesthesia	18(4.0%)	2(0.4%)	71(9.4%)	3(0.4%)	89(7.4%)	5(0.4%)
Parosmia			3(0.4%)		3(0.2%)	
Peripheral motor neuropathy	3(0.7%)		3(0.4%)	1(0.1%)	6(0.5%)	1(0.1%)
Peripheral sensory neuropathy	20(4.4%)	2(0.4%)	22(2.9%)	1(0.1%)	42(3.5%)	3(0.2%)
Peroneal nerve palsy			1(0.1%)		1(0.1%)	
Restless legs syndrome			1(0.1%)		1(0.1%)	
Sinus headache			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Somnolence			1(0.1%)		1(0.1%)	
Syncope	4(0.9%)	4(0.9%)	1(0.1%)		5(0.4%)	4(0.3%)
Syncope vasovagal	1(0.2%)	1(0.2%)	2(0.3%)		3(0.2%)	1(0.1%)
Tremor	2(0.4%)				2(0.2%)	
Trigeminal neuralgia			1(0.1%)		1(0.1%)	
Psychiatric disorders	35(7.8%)	4(0.9%)	40(5.3%)	9(1.2%)	75(6.2%)	13(1.1%)
Agitation			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Anxiety	5(1.1%)		9(1.2%)	2(0.3%)	14(1.2%)	2(0.2%)
Confusional state	2(0.4%)	2(0.4%)	7(0.9%)	4(0.5%)	9(0.7%)	6(0.5%)
Depressed mood			2(0.3%)		2(0.2%)	
Depression	4(0.9%)		1(0.1%)		5(0.4%)	
Disorientation	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Emotional disorder			1(0.1%)		1(0.1%)	
Insomnia	22(4.9%)	1(0.2%)	22(2.9%)	3(0.4%)	44(3.7%)	4(0.3%)
Mood altered			1(0.1%)		1(0.1%)	
Nervousness			1(0.1%)		1(0.1%)	
Restlessness	1(0.2%)		2(0.3%)		3(0.2%)	
Sleep disorder	1(0.2%)				1(0.1%)	
Renal and urinary disorders	10(2.2%)	1(0.2%)	8(1.1%)	2(0.3%)	18(1.5%)	3(0.2%)
Dysuria	2(0.4%)		2(0.3%)		4(0.3%)	
Haematuria	4(0.9%)		1(0.1%)		5(0.4%)	

Table 40 continued

MedDRA class - n (%)	VFL UTC (N=450)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
Haemoglobinuria			1(0.1%)		1(0.1%)	
Micturition disorder	1(0.2%)				1(0.1%)	
Nocturia	1(0.2%)				1(0.1%)	
Pollakiuria	1(0.2%)		1(0.1%)		2(0.2%)	
Renal colic	1(0.2%)				1(0.1%)	
Renal failure	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Renal pain			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Renal tubular necrosis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Urinary incontinence			1(0.1%)		1(0.1%)	
Reproductive system and breast disorders	7(1.6%)	2(0.4%)	3(0.4%)		10(0.8%)	2(0.2%)
Erectile dysfunction			1(0.1%)		1(0.1%)	
Pelvic pain	6(1.3%)	2(0.4%)	2(0.3%)		8(0.7%)	2(0.2%)
Penile discharge	1(0.2%)				1(0.1%)	
Penile pain	1(0.2%)				1(0.1%)	
Respiratory, thoracic and mediastinal disorders	44(9.8%)	9(2.0%)	52(6.9%)	17(2.3%)	96(8.0%)	26(2.2%)
Acute respiratory distress syndrome	1(0.2%)	1(0.2%)	2(0.3%)	2(0.3%)	3(0.2%)	3(0.2%)
Bronchospasm			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Cough	10(2.2%)		8(1.1%)		18(1.5%)	
Cryptogenic organising pneumonia	2(0.4%)	1(0.2%)			2(0.2%)	1(0.1%)
Dry throat			1(0.1%)		1(0.1%)	
Dysphonia	2(0.4%)		3(0.4%)		5(0.4%)	
Dyspnoea	16(3.6%)	2(0.4%)	24(3.2%)	13(1.7%)	40(3.3%)	15(1.2%)
Dyspnoea exertional	3(0.7%)				3(0.2%)	
Epistaxis	5(1.1%)	1(0.2%)	7(0.9%)		12(1.0%)	1(0.1%)
Haemoptysis	1(0.2%)		2(0.3%)		3(0.2%)	
Hiccups	2(0.4%)		2(0.3%)		4(0.3%)	
Hypoxia			1(0.1%)		1(0.1%)	
Interstitial lung disease			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Lung disorder	1(0.2%)				1(0.1%)	
Pharyngolaryngeal pain	4(0.9%)		4(0.5%)		8(0.7%)	
Pleural effusion			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Pneumonitis	1(0.2%)				1(0.1%)	
Productive cough	2(0.4%)		1(0.1%)		3(0.2%)	
Pulmonary embolism	3(0.7%)	3(0.7%)	1(0.1%)	1(0.1%)	4(0.3%)	4(0.3%)
Pulmonary oedema	1(0.2%)	1(0.2%)			1(0.1%)	1(0.1%)
Respiratory disorder			1(0.1%)		1(0.1%)	
Respiratory failure			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Rhinorrhoea			1(0.1%)		1(0.1%)	
Skin and subcutaneous tissue disorders	155(34.4%)		249(33.1%)	1(0.1%)	404(33.6%)	1(0.1%)
Acne	1(0.2%)				1(0.1%)	
Alopecia	129(28.7%)		220(29.2%)		349(29.0%)	
Blister	1(0.2%)				1(0.1%)	
Dermatitis exfoliative	1(0.2%)				1(0.1%)	
Dry skin	4(0.9%)		5(0.7%)		9(0.7%)	
Erythema	2(0.4%)		1(0.1%)		3(0.2%)	
Hyperhidrosis	5(1.1%)		8(1.1%)		13(1.1%)	
Hypotrichosis	1(0.2%)				1(0.1%)	
Nail disorder	1(0.2%)		3(0.4%)		4(0.3%)	
Night sweats	1(0.2%)		1(0.1%)		2(0.2%)	
Pain of skin	1(0.2%)		2(0.3%)		3(0.2%)	
Palmar-plantar erythrodysaesthesia syndrome	1(0.2%)		1(0.1%)		2(0.2%)	
Pigmentation disorder	1(0.2%)		2(0.3%)		3(0.2%)	
Pruritus	6(1.3%)		13(1.7%)		19(1.6%)	
Pruritus generalised	1(0.2%)		1(0.1%)		2(0.2%)	
Purpura	1(0.2%)				1(0.1%)	
Rash	7(1.6%)		13(1.7%)		20(1.7%)	
Rash macular			1(0.1%)		1(0.1%)	
Rash papular			1(0.1%)		1(0.1%)	

-	Skin exfoliation	1(0.2%)			1(0.1%)	
-	Skin lesion	1(0.2%)		1(0.1%)	2(0.2%)	
-	Skin necrosis			1(0.1%)	1(0.1%)	1(0.1%)
-	Skin ulcer			1(0.1%)	1(0.1%)	
-	Urticaria	6(1.3%)		4(0.5%)	10(0.8%)	
Vascular disorders		42(9.3%)	13(2.5%)	49(6.5%)	91(7.6%)	26(2.2%)
-	Arteriopathic disease	1(0.2%)			1(0.1%)	
-	Deep vein thrombosis	2(0.4%)	2(0.4%)		2(0.2%)	2(0.2%)
-	Flushing	2(0.4%)		8(1.1%)	10(0.8%)	
-	Hot flush	1(0.2%)		8(1.1%)	9(0.7%)	
-	Hypertension	15(3.3%)	8(1.6%)	19(2.5%)	34(2.8%)	18(1.5%)
-	Hypertensive crisis			1(0.1%)	1(0.1%)	1(0.1%)
-	Hypotension	5(1.1%)	1(0.2%)	4(0.5%)	9(0.7%)	3(0.2%)
-	Hypovolaemic shock	1(0.2%)	1(0.2%)		1(0.1%)	1(0.1%)
-	Ischaemia	1(0.2%)	1(0.2%)		1(0.1%)	1(0.1%)
-	Lymphoedema	3(0.7%)		2(0.3%)	5(0.4%)	
-	Orthostatic hypotension	1(0.2%)	1(0.2%)	1(0.1%)	2(0.2%)	2(0.2%)
-	Phlebitis	10(2.2%)		4(0.5%)	14(1.2%)	
-	Phlebitis superficial	1(0.2%)		2(0.3%)	3(0.2%)	
-	Thrombophlebitis	1(0.2%)		1(0.1%)	2(0.2%)	
-	Thrombophlebitis superficial	1(0.2%)			1(0.1%)	
-	Vasculitis	1(0.2%)		1(0.1%)	2(0.2%)	
-	Vasospasm	1(0.2%)			1(0.1%)	

Table 41: Incidence in term of patients of study treatment-related adverse events by system organ class and preferred term at 320 mg/m² - VFL TCCU (UTC) and VFL Non-TCCU

MedDRA class - n (%)	VFL UTC (N=272)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
ANY ADVERSE EVENT	255(93.8%)	120(44.1%)	676(89.8%)	281(37.3%)	1096(91.1%)	501(41.6%)
Blood and lymphatic system disorders	21(7.7%)	20(7.4%)	34(4.5%)	33(4.4%)	67(5.6%)	65(5.4%)
- Disseminated intravascular coagulation					1(0.1%)	1(0.1%)
- Febrile neutropenia	19(7.0%)	19(7.0%)	34(4.5%)	33(4.4%)	64(5.3%)	63(5.2%)
- Pancytopenia	2(0.7%)	1(0.4%)			2(0.2%)	1(0.1%)
Cardiac disorders	9(3.3%)	4(1.5%)	15(2.0%)	3(0.4%)	29(2.4%)	9(0.7%)
- Arrhythmia supraventricular			1(0.1%)		1(0.1%)	
- Atrial fibrillation			1(0.1%)		1(0.1%)	
- Bradycardia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Cardiac failure			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Cardio-respiratory arrest	1(0.4%)	1(0.4%)			1(0.1%)	1(0.1%)
- Cardiogenic shock			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Myocardial infarction			1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
- Myocardial ischaemia	2(0.7%)	2(0.7%)	2(0.3%)	1(0.1%)	5(0.4%)	4(0.3%)
- Palpitations	2(0.7%)		4(0.5%)		6(0.5%)	
- Sinus tachycardia	1(0.4%)	1(0.4%)	1(0.1%)		4(0.3%)	1(0.1%)
- Supraventricular extrasystoles	1(0.4%)				1(0.1%)	
- Tachycardia	2(0.7%)		4(0.5%)		7(0.6%)	
Ear and labyrinth disorders	9(3.3%)	1(0.4%)	31(4.1%)	2(0.3%)	45(3.7%)	4(0.3%)
- Deafness			1(0.1%)		1(0.1%)	
- Ear pain	4(1.5%)		12(1.6%)	1(0.1%)	18(1.5%)	1(0.1%)
- Tinnitus	3(1.1%)		6(0.8%)		10(0.8%)	
- Vertigo	2(0.7%)	1(0.4%)	14(1.9%)	1(0.1%)	17(1.4%)	3(0.2%)
- Vertigo positional					1(0.1%)	
Endocrine disorders			3(0.4%)	3(0.4%)	3(0.2%)	3(0.2%)
- Inappropriate antidiuretic hormone secretion			3(0.4%)	3(0.4%)	3(0.2%)	3(0.2%)
Eye disorders	4(1.5%)		28(3.7%)	1(0.1%)	33(2.7%)	2(0.2%)
- Blindness			1(0.1%)		1(0.1%)	
- Conjunctivitis			2(0.3%)		2(0.2%)	

MedDRA class - n (%)	VFL UTC (N=272)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Diplopia			1(0.1%)		1(0.1%)	
- Dry eye	1(0.4%)				1(0.1%)	
- Eye pain			1(0.1%)		1(0.1%)	
- Eyelid ptosis			1(0.1%)		1(0.1%)	
- Eyelids pruritus			1(0.1%)		1(0.1%)	
- Keratoconjunctivitis sicca			1(0.1%)		1(0.1%)	
- Lacrimation increased			4(0.5%)		4(0.3%)	
- Ocular discomfort			1(0.1%)		1(0.1%)	
- Photopsia			1(0.1%)		1(0.1%)	
- Retinal vein thrombosis					1(0.1%)	1(0.1%)
- Vision blurred	1(0.4%)		16(2.1%)	1(0.1%)	17(1.4%)	1(0.1%)
- Visual acuity reduced	1(0.4%)				1(0.1%)	
- Visual disturbance			1(0.1%)		1(0.1%)	
- Vitreous floaters	1(0.4%)				1(0.1%)	
Gastrointestinal disorders	219(80.5%)	56(20.6%)	591(78.5%)	146(19.4%)	954(79.3%)	257(21.4%)
- Abdominal discomfort	2(0.7%)		2(0.3%)		5(0.4%)	1(0.1%)
- Abdominal distension	3(1.1%)		4(0.5%)	1(0.1%)	9(0.7%)	1(0.1%)
- Abdominal pain	47(17.3%)	7(2.6%)	200(26.6%)	44(5.8%)	276(22.9%)	62(5.2%)
- Abdominal pain lower	2(0.7%)		1(0.1%)		4(0.3%)	
- Abdominal pain upper	16(5.9%)	2(0.7%)	48(6.4%)	3(0.4%)	66(5.5%)	6(0.5%)
- Abdominal tenderness			2(0.3%)		2(0.2%)	
- Anal discomfort			1(0.1%)		1(0.1%)	
- Anal fistula			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Anal haemorrhage					1(0.1%)	
- Aptyalism			1(0.1%)		1(0.1%)	
- Cheilitis			1(0.1%)		1(0.1%)	
- Colonic pseudo-obstruction					1(0.1%)	1(0.1%)
- Constipation	146(53.7%)	36(13.2%)	405(53.8%)	75(10.0%)	652(54.2%)	144(12.0%)
- Diarrhoea	32(11.8%)	1(0.4%)	85(11.3%)	7(0.5%)	143(11.9%)	11(0.5%)

Table 41 continued

	Dry mouth	4(1.5%)		11(1.5%)		17(1.4%)	
	Dyspepsia	17(6.3%)		32(4.2%)	1(0.1%)	57(4.7%)	2(0.2%)
	Dysphagia	4(1.5%)	1(0.4%)	13(1.7%)	4(0.5%)	22(1.8%)	6(0.5%)
	Epigastric discomfort			1(0.1%)		2(0.2%)	
	Eructation	2(0.7%)		1(0.1%)		3(0.2%)	
	Faecal incontinence					1(0.1%)	
	Faeces discoloured	1(0.4%)				1(0.1%)	
	Flatulence	7(2.6%)		21(2.8%)		30(2.5%)	
	Gastric ulcer haemorrhage	1(0.4%)				1(0.1%)	
	Gastritis	2(0.7%)		9(1.2%)	1(0.1%)	11(0.9%)	1(0.1%)
	Gingival bleeding					1(0.1%)	
	Gingival pain	2(0.7%)		1(0.1%)		3(0.2%)	
	Glossodynia	2(0.7%)		4(0.5%)		6(0.5%)	
	Haematemesis	1(0.4%)		1(0.1%)		3(0.2%)	1(0.1%)
	Haemorrhoids					3(0.2%)	
	Hypoaesthesia oral			2(0.3%)		2(0.2%)	
	Ileus	3(1.1%)	2(0.7%)	14(1.9%)	10(1.3%)	25(2.1%)	20(1.7%)
	Ileus paralytic	1(0.4%)	1(0.4%)			2(0.2%)	2(0.2%)
	Intestinal obstruction	1(0.4%)				1(0.1%)	
	Intestinal spasm			1(0.1%)		1(0.1%)	
	Lip blister			1(0.1%)		1(0.1%)	
	Lip dry					1(0.1%)	
	Lip swelling			1(0.1%)		1(0.1%)	
	Melaena	1(0.4%)				2(0.2%)	1(0.1%)
	Mouth ulceration			1(0.1%)		2(0.2%)	
	Nausea	108(39.7%)	4(1.5%)	323(42.9%)	22(2.9%)	507(42.1%)	35(2.9%)
	Odynophagia	2(0.7%)	1(0.4%)	3(0.4%)		5(0.4%)	1(0.1%)
	Oesophagitis	1(0.4%)	1(0.4%)	1(0.1%)		3(0.2%)	1(0.1%)
	Oral discomfort					1(0.1%)	
	Oral mucosal disorder	1(0.4%)				1(0.1%)	
	Oral pain	6(2.2%)	1(0.4%)	10(1.3%)	2(0.3%)	16(1.3%)	3(0.2%)
	Pancreatitis	1(0.4%)	1(0.4%)			1(0.1%)	1(0.1%)
	Paraesthesia oral	2(0.7%)		3(0.4%)		6(0.5%)	
	Proctalgia	1(0.4%)				1(0.1%)	
	Retching	2(0.7%)				2(0.2%)	
	Saliva altered	1(0.4%)				1(0.1%)	
	Salivary gland disorder			1(0.1%)		1(0.1%)	
	Salivary hypersecretion			2(0.3%)		2(0.2%)	
	Small intestinal obstruction			1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
	Stomatitis	82(30.1%)	9(3.3%)	267(35.5%)	13(1.7%)	388(32.3%)	25(2.1%)
	Subileus	1(0.4%)				1(0.1%)	
	Swollen tongue	2(0.7%)		3(0.4%)		6(0.5%)	
	Tongue blistering	1(0.4%)				1(0.1%)	
	Tongue disorder			1(0.1%)		1(0.1%)	
	Tongue ulceration			3(0.4%)		3(0.2%)	
	Toothache			1(0.1%)		2(0.2%)	
	Vomiting	67(24.6%)	7(2.6%)	233(30.9%)	22(2.9%)	356(29.6%)	35(2.9%)
General disorders and administration site conditions		201(73.9%)	43(15.8%)	511(67.9%)	108(14.3%)	836(69.5%)	188(15.6%)
	Asthenia	8(2.9%)	1(0.4%)	5(0.7%)	2(0.3%)	25(2.1%)	7(0.6%)
	Catheter site rash			1(0.1%)		1(0.1%)	
	Chest discomfort			2(0.3%)		2(0.2%)	
	Chest pain	10(3.7%)	2(0.7%)	39(5.2%)	9(1.2%)	54(4.5%)	12(1.0%)
	Chills	8(2.9%)		17(2.3%)		27(2.2%)	1(0.1%)
	Condition aggravated	1(0.4%)	1(0.4%)	4(0.5%)	2(0.3%)	5(0.4%)	3(0.2%)
	Early satiety					1(0.1%)	
	Extravasation	1(0.4%)		2(0.3%)		5(0.4%)	
	Facial pain	1(0.4%)				1(0.1%)	
	Fatigue	147(54.0%)	38(14.0%)	414(55.0%)	89(11.8%)	647(53.8%)	155(12.9%)

MedDRA class - n (%)	VFL UTC (N=272)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
Inflammation					1(0.1%)	
Influenza like illness	1(0.4%)		3(0.4%)		6(0.5%)	
Infusion related reaction	3(1.1%)				5(0.4%)	
Infusion site erythema			8(1.1%)		9(0.7%)	
Infusion site pain	6(2.2%)		25(3.3%)	1(0.1%)	35(2.9%)	1(0.1%)
Infusion site phlebitis	1(0.4%)		4(0.5%)		5(0.4%)	
Infusion site reaction	2(0.7%)		49(6.5%)		54(4.5%)	
Infusion site swelling			1(0.1%)		1(0.1%)	
Injection site anaesthesia			1(0.1%)		1(0.1%)	
Injection site erythema	1(0.4%)		3(0.4%)		9(0.7%)	
Injection site hypersensitivity	1(0.4%)				1(0.1%)	
Injection site irritation	6(2.2%)		1(0.1%)		7(0.6%)	
Injection site pain	10(3.7%)		5(0.7%)		25(2.1%)	
Injection site phlebitis	4(1.5%)		4(0.5%)		15(1.2%)	
Injection site pruritus	1(0.4%)		1(0.1%)		4(0.3%)	
Injection site rash	1(0.4%)				2(0.2%)	
Injection site reaction	46(16.9%)	2(0.7%)	88(11.7%)	2(0.3%)	166(13.8%)	4(0.3%)
Injection site swelling			1(0.1%)		1(0.1%)	
Injection site urticaria			1(0.1%)		3(0.2%)	
Injection site vesicles			1(0.1%)		1(0.1%)	
Local swelling			1(0.1%)		1(0.1%)	
Malaise	2(0.7%)		1(0.1%)		3(0.2%)	
Mucosal inflammation			1(0.1%)		1(0.1%)	
Non-cardiac chest pain	1(0.4%)				1(0.1%)	
Oedema	1(0.4%)		3(0.4%)		4(0.3%)	
Oedema peripheral	3(1.1%)		2(0.3%)		7(0.6%)	
Pain	13(4.8%)		13(1.7%)	7(0.9%)	29(2.4%)	8(0.7%)
Peripheral coldness	1(0.4%)		1(0.1%)		2(0.2%)	
Pyrexia	26(9.6%)		71(9.4%)	6(0.8%)	120(10.0%)	9(0.7%)

Table 41 continued

Hepatobiliary disorders	1(0.4%)		1(0.1%)		2(0.2%)	
Hepatic pain	1(0.4%)		1(0.1%)		2(0.2%)	
Immune system disorders	5(1.8%)		12(1.6%)	2(0.3%)	21(1.7%)	3(0.2%)
Hypersensitivity	4(1.5%)		12(1.6%)	2(0.3%)	20(1.7%)	3(0.2%)
Seasonal allergy	1(0.4%)				1(0.1%)	
Infections and infestations	30(11.0%)	17(6.3%)	70(9.3%)	35(4.6%)	115(9.6%)	65(5.4%)
Abscess	1(0.4%)	1(0.4%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Bacteraemia	1(0.4%)	1(0.4%)			1(0.1%)	1(0.1%)
Bronchitis	2(0.7%)		4(0.5%)	1(0.1%)	6(0.5%)	1(0.1%)
Bronchitis acute			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Candidiasis	4(1.5%)				4(0.3%)	
Catheter related infection			1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Cellulitis			2(0.3%)	2(0.3%)	2(0.2%)	2(0.2%)
Cystitis	1(0.4%)		1(0.1%)		2(0.2%)	
Ear infection			1(0.1%)		1(0.1%)	
Escherichia sepsis					1(0.1%)	1(0.1%)
Herpes simplex			5(0.7%)	1(0.1%)	5(0.4%)	1(0.1%)
Herpes virus infection	1(0.4%)				1(0.1%)	
Hordeolum			1(0.1%)		1(0.1%)	
Infection	2(0.7%)	1(0.4%)	5(0.7%)	3(0.4%)	7(0.6%)	4(0.3%)
Influenza			1(0.1%)		1(0.1%)	
Injection site infection			1(0.1%)		1(0.1%)	
Laryngopharyngitis			1(0.1%)		1(0.1%)	
Lobar pneumonia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Lower respiratory tract infection			2(0.3%)	1(0.1%)	2(0.2%)	1(0.1%)
Lung infection			2(0.3%)	2(0.3%)	2(0.2%)	2(0.2%)
Nasopharyngitis	1(0.4%)		1(0.1%)		2(0.2%)	
Neutropenic infection	8(2.9%)	8(2.9%)	8(1.1%)	8(1.1%)	25(2.1%)	25(2.1%)
Neutropenic sepsis			3(0.4%)	3(0.4%)	4(0.3%)	4(0.3%)

Oral candidiasis	2(0.7%)		4(0.5%)		6(0.5%)	
Oral infection	1(0.4%)		2(0.3%)	1(0.1%)	4(0.3%)	2(0.2%)
Pharyngitis			6(0.8%)	1(0.1%)	6(0.5%)	1(0.1%)
Pneumonia	4(1.5%)	4(1.5%)	3(0.4%)	1(0.1%)	9(0.7%)	6(0.5%)
Pyelonephritis					1(0.1%)	
Rhinitis			1(0.1%)		1(0.1%)	
Sepsis	1(0.4%)	1(0.4%)	1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Septic shock	1(0.4%)	1(0.4%)	3(0.4%)	3(0.4%)	4(0.3%)	4(0.3%)
Tonsillitis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Tooth infection			1(0.1%)		1(0.1%)	
Upper respiratory tract infection	2(0.7%)		4(0.5%)		6(0.5%)	
Urinary tract infection	4(1.5%)	1(0.4%)	6(0.8%)	4(0.5%)	13(1.1%)	6(0.5%)
Vaginal candidiasis			1(0.1%)		1(0.1%)	
Viral infection			1(0.1%)		1(0.1%)	
Wound infection			1(0.1%)		2(0.2%)	
Injury, poisoning and procedural complications	4(1.5%)	1(0.4%)	2(0.3%)		6(0.5%)	1(0.1%)
Collapse of lung			1(0.1%)		1(0.1%)	
Contusion			1(0.1%)		1(0.1%)	
Fall	3(1.1%)	1(0.4%)			3(0.2%)	1(0.1%)
Ureterostomy site discomfort	1(0.4%)				1(0.1%)	
Investigations	69(25.4%)	2(0.7%)	141(18.7%)	7(0.9%)	251(20.9%)	10(0.8%)
Alanine aminotransferase increased	1(0.4%)		1(0.1%)	1(0.1%)	3(0.2%)	1(0.1%)
Aspartate aminotransferase increased			1(0.1%)		2(0.2%)	
Electrocardiogram ST segment abnormal	1(0.4%)				1(0.1%)	
Electrocardiogram T wave abnormal			1(0.1%)		1(0.1%)	
Gamma-glutamyltransferase increased			4(0.5%)	3(0.4%)	4(0.3%)	3(0.2%)
Neutrophil count increased	1(0.4%)	1(0.4%)			1(0.1%)	1(0.1%)
Troponin I increased			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Weight decreased	68(25.0%)	1(0.4%)	135(17.9%)	2(0.3%)	243(20.2%)	4(0.3%)

MedDRA class - n (%)	VFL UTC (N=272)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
Weight increased	1(0.4%)				1(0.1%)	
Metabolism and nutrition disorders	97(35.7%)	14(5.1%)	183(24.3%)	21(2.8%)	353(29.3%)	43(3.6%)
Acidosis					1(0.1%)	
Anorexia	91(33.5%)	8(2.9%)	176(23.4%)	14(1.9%)	331(27.5%)	26(2.2%)
Dehydration	13(4.8%)	6(2.2%)	11(1.5%)	7(0.9%)	31(2.6%)	16(1.3%)
Gout					1(0.1%)	
Hyperglycaemia	1(0.4%)	1(0.4%)	2(0.3%)	2(0.3%)	5(0.4%)	5(0.4%)
Hypoalbuminaemia	1(0.4%)				1(0.1%)	
Hypoglycaemia	1(0.4%)	1(0.4%)	1(0.1%)		2(0.2%)	1(0.1%)
Hypomagnesaemia	1(0.4%)				2(0.2%)	
Hypovolaemia					1(0.1%)	1(0.1%)
Musculoskeletal and connective tissue disorders	105(38.6%)	17(6.3%)	254(33.7%)	42(5.6%)	401(33.3%)	67(5.6%)
Arthralgia	20(7.4%)	2(0.7%)	74(9.8%)	11(1.5%)	106(8.8%)	14(1.2%)
Back pain	17(6.3%)	2(0.7%)	19(2.5%)	2(0.3%)	41(3.4%)	4(0.3%)
Bone pain	10(3.7%)		19(2.5%)	6(0.8%)	30(2.5%)	6(0.5%)
Flank pain	3(1.1%)		2(0.3%)	1(0.1%)	5(0.4%)	1(0.1%)
Groin pain	1(0.4%)		1(0.1%)		3(0.2%)	1(0.1%)
Joint stiffness	1(0.4%)				1(0.1%)	
Muscle contracture	1(0.4%)				1(0.1%)	
Muscle spasms	6(2.2%)		6(0.8%)		14(1.2%)	
Muscular weakness	4(1.5%)	1(0.4%)	17(2.3%)	2(0.3%)	27(2.2%)	6(0.5%)
Musculoskeletal chest pain	4(1.5%)	1(0.4%)	1(0.1%)		6(0.5%)	1(0.1%)
Musculoskeletal discomfort			1(0.1%)		1(0.1%)	
Musculoskeletal pain	7(2.6%)		4(0.5%)	1(0.1%)	13(1.1%)	1(0.1%)
Musculoskeletal stiffness	1(0.4%)		1(0.1%)	1(0.1%)	2(0.2%)	1(0.1%)
Myalgia	54(19.9%)	11(4.0%)	146(19.4%)	26(3.5%)	220(18.3%)	40(3.3%)
Myositis			1(0.1%)		1(0.1%)	
Neck pain	5(1.8%)		5(0.7%)		12(1.0%)	
Pain in extremity	12(4.4%)		13(1.7%)	1(0.1%)	28(2.3%)	1(0.1%)

Table 41 continued

- Pain in jaw	10(3.7%)		50(6.6%)	6(0.8%)	65(5.4%)	6(0.5%)
- Polyarthritis			1(0.1%)		1(0.1%)	
- Trismus	1(0.4%)		1(0.1%)		2(0.2%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4(1.5%)	1(0.4%)	17(2.3%)	4(0.5%)	23(1.9%)	5(0.4%)
- Cancer pain	4(1.5%)	1(0.4%)	16(2.1%)	4(0.5%)	21(1.7%)	5(0.4%)
- Metastatic pain			2(0.3%)		3(0.2%)	
Nervous system disorders	77(28.3%)	10(3.7%)	210(27.9%)	17(2.3%)	328(27.3%)	34(2.8%)
- Ageusia					1(0.1%)	
- Akinaesthesia			1(0.1%)		1(0.1%)	
- Amnesia			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Aphonia			2(0.3%)		2(0.2%)	
- Areflexia			3(0.4%)		3(0.2%)	
- Burning sensation			2(0.3%)		2(0.2%)	
- Convulsion			2(0.3%)	2(0.3%)	3(0.2%)	3(0.2%)
- Coordination Abnormal			1(0.1%)		1(0.1%)	
- Depressed level of consciousness			1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
- Disturbance in attention			2(0.3%)		2(0.2%)	
- Dizziness	16(5.9%)	1(0.4%)	27(3.6%)	2(0.3%)	51(4.2%)	4(0.3%)
- Dysaesthesia			1(0.1%)		1(0.1%)	
- Dysgeusia	6(2.2%)		24(3.2%)		37(3.1%)	
- Dysphasia			1(0.1%)		1(0.1%)	
- Extrapyramidal disorder			2(0.3%)	1(0.1%)	2(0.2%)	1(0.1%)
- Headache	20(7.4%)	2(0.7%)	65(8.6%)	4(0.5%)	93(7.7%)	7(0.6%)
- Hyperaesthesia	1(0.4%)				1(0.1%)	
- Hypersomnia					1(0.1%)	
- Hypoaesthesia	5(1.8%)		8(1.1%)		15(1.2%)	
- Lethargy	2(0.7%)		2(0.3%)		4(0.3%)	
- Neuralgia	18(6.6%)	1(0.4%)	34(4.5%)	4(0.5%)	61(5.1%)	6(0.5%)
- Neuropathy	4(1.5%)				5(0.4%)	
- Neuropathy peripheral	4(1.5%)				4(0.3%)	
- Paraesthesia	12(4.4%)	1(0.4%)	71(9.4%)	3(0.4%)	89(7.4%)	5(0.4%)
- Parosmia			3(0.4%)		3(0.2%)	
- Peripheral motor neuropathy	2(0.7%)		3(0.4%)	1(0.1%)	6(0.5%)	1(0.1%)
- Peripheral sensory neuropathy	16(5.9%)	1(0.4%)	22(2.9%)	1(0.1%)	42(3.5%)	3(0.2%)
- Peroneal nerve palsy			1(0.1%)		1(0.1%)	
- Restless legs syndrome			1(0.1%)		1(0.1%)	
- Sinus headache			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Somnolence			1(0.1%)		1(0.1%)	
- Syncope	4(1.5%)	4(1.5%)	1(0.1%)		5(0.4%)	4(0.3%)
- Syncope vasovagal	1(0.4%)	1(0.4%)	2(0.3%)		3(0.2%)	1(0.1%)
- Tremor	1(0.4%)				2(0.2%)	
- Trigeminal neuralgia			1(0.1%)		1(0.1%)	
Psychiatric disorders	17(6.3%)	2(0.7%)	40(5.3%)	9(1.2%)	75(6.2%)	13(1.1%)
- Agitation			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Anxiety	2(0.7%)		9(1.2%)	2(0.3%)	14(1.2%)	2(0.2%)
- Confusional state	1(0.4%)	1(0.4%)	7(0.9%)	4(0.5%)	9(0.7%)	6(0.5%)
- Depressed mood			2(0.3%)		2(0.2%)	
- Depression	2(0.7%)		1(0.1%)		5(0.4%)	
- Disorientation					1(0.1%)	1(0.1%)
- Emotional disorder			1(0.1%)		1(0.1%)	
- Insomnia	12(4.4%)	1(0.4%)	22(2.9%)	3(0.4%)	44(3.7%)	4(0.3%)
- Mood altered			1(0.1%)		1(0.1%)	
- Nervousness			1(0.1%)		1(0.1%)	
- Restlessness			2(0.3%)		3(0.2%)	
- Sleep disorder					1(0.1%)	
Renal and urinary disorders	7(2.6%)		8(1.1%)	2(0.3%)	18(1.5%)	3(0.2%)
- Dysuria	2(0.7%)		2(0.3%)		4(0.3%)	
- Haematuria	3(1.1%)		1(0.1%)		5(0.4%)	

MedDRA class - n (%)	VFL UTC (N=272)		VFL ALL1 (N=753)		ALL VFL (N=1203)	
SYSTEM ORGAN / PREFERRED TERM	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4	ANY GRADE	SEVERE 3-4
- Haemoglobinuria			1(0.1%)		1(0.1%)	
- Micturition disorder					1(0.1%)	
- Nocturia	1(0.4%)				1(0.1%)	
- Pollakiuria	1(0.4%)		1(0.1%)		2(0.2%)	
- Renal colic	1(0.4%)				1(0.1%)	
- Renal failure					1(0.1%)	1(0.1%)
- Renal pain			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Renal tubular necrosis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Urinary incontinence			1(0.1%)		1(0.1%)	
Reproductive system and breast disorders	3(1.1%)	1(0.4%)	3(0.4%)		10(0.8%)	2(0.2%)
- Erectile dysfunction			1(0.1%)		1(0.1%)	
- Pelvic pain	2(0.7%)	1(0.4%)	2(0.3%)		8(0.7%)	2(0.2%)
- Penile discharge	1(0.4%)				1(0.1%)	
- Penile pain					1(0.1%)	
Respiratory, thoracic and mediastinal disorders	23(8.5%)	3(1.1%)	82(6.9%)	17(2.3%)	96(8.0%)	26(2.2%)
- Acute respiratory distress syndrome			2(0.3%)	2(0.3%)	3(0.2%)	3(0.2%)
- Bronchospasm			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Cough	6(2.2%)		8(1.1%)		18(1.5%)	
- Cryptogenic organising pneumonia	1(0.4%)	1(0.4%)			2(0.2%)	1(0.1%)
- Dry throat			1(0.1%)		1(0.1%)	
- Dysphonia	2(0.7%)		3(0.4%)		5(0.4%)	
- Dyspnoea	8(2.9%)		24(3.2%)	13(1.7%)	40(3.3%)	15(1.2%)
- Dyspnoea exertional	1(0.4%)				3(0.2%)	
- Epistaxis	2(0.7%)		7(0.9%)		12(1.0%)	1(0.1%)
- Haemoptysis	1(0.4%)		2(0.3%)		3(0.2%)	
- Hiccups	2(0.7%)		2(0.3%)		4(0.3%)	
- Hypoxia			1(0.1%)		1(0.1%)	
- Interstitial lung disease			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
- Lung disorder					1(0.1%)	

Table 41 continued

Pharyngolaryngeal pain	4(1.5%)		4(0.5%)		8(0.7%)	
Pleural effusion			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Pneumonitis	1(0.4%)				1(0.1%)	
Productive cough	1(0.4%)		1(0.1%)		3(0.2%)	
Pulmonary embolism	1(0.4%)	1(0.4%)	1(0.1%)	1(0.1%)	4(0.3%)	4(0.3%)
Pulmonary oedema	1(0.4%)	1(0.4%)			1(0.1%)	1(0.1%)
Respiratory disorder			1(0.1%)		1(0.1%)	
Respiratory failure			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Rhinorrhoea			1(0.1%)		1(0.1%)	
Skin and subcutaneous tissue disorders	102(37.5%)		249(33.1%)	1(0.1%)	404(33.6%)	1(0.1%)
Acne	1(0.4%)				1(0.1%)	
Alopecia	88(32.4%)		220(29.2%)		349(29.0%)	
Blister	1(0.4%)				1(0.1%)	
Dermatitis exfoliative					1(0.1%)	
Dry skin	3(1.1%)		5(0.7%)		9(0.7%)	
Erythema	1(0.4%)		1(0.1%)		3(0.2%)	
Hyperhidrosis	4(1.5%)		8(1.1%)		13(1.1%)	
Hypotrichosis					1(0.1%)	
Nail disorder	1(0.4%)		3(0.4%)		4(0.3%)	
Night sweats	1(0.4%)		1(0.1%)		2(0.2%)	
Pain of skin			2(0.3%)		3(0.2%)	
Palmar-plantar erythrodysaesthesia syndrome			1(0.1%)		2(0.2%)	
Pigmentation disorder			2(0.3%)		3(0.2%)	
Pruritus	5(1.8%)		13(1.7%)		19(1.6%)	
Pruritus generalised	1(0.4%)		1(0.1%)		2(0.2%)	
Purpura	1(0.4%)				1(0.1%)	
Rash	5(1.8%)		13(1.7%)		20(1.7%)	
Rash macular			1(0.1%)		1(0.1%)	
Rash papular			1(0.1%)		1(0.1%)	
Skin exfoliation					1(0.1%)	
Skin lesion	1(0.4%)		1(0.1%)		2(0.2%)	
Skin necrosis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Skin ulcer			1(0.1%)		1(0.1%)	
Urticaria	4(1.5%)		4(0.5%)		10(0.8%)	
Vascular disorders	24(8.8%)	4(1.5%)	49(6.5%)	13(1.7%)	91(7.6%)	26(2.2%)
Arteriopathic disease	1(0.4%)				1(0.1%)	
Deep vein thrombosis	1(0.4%)	1(0.4%)			2(0.2%)	2(0.2%)
Flushing	2(0.7%)		8(1.1%)		10(0.8%)	
Hot flush			8(1.1%)		9(0.7%)	
Hypertension	7(2.6%)	2(0.7%)	19(2.5%)	10(1.3%)	34(2.8%)	18(1.5%)
Hypertensive crisis			1(0.1%)	1(0.1%)	1(0.1%)	1(0.1%)
Hypotension	3(1.1%)	1(0.4%)	4(0.5%)	2(0.3%)	9(0.7%)	3(0.2%)
Hypovolaemic shock					1(0.1%)	1(0.1%)
Ischaemia					1(0.1%)	1(0.1%)
Lymphoedema	2(0.7%)		2(0.3%)		5(0.4%)	
Orthostatic hypotension			1(0.1%)	1(0.1%)	2(0.2%)	2(0.2%)
Phlebitis	7(2.6%)		4(0.5%)		14(1.2%)	
Phlebitis superficial	1(0.4%)		2(0.3%)		3(0.2%)	
Thrombophlebitis	1(0.4%)		1(0.1%)		2(0.2%)	
Thrombophlebitis superficial	1(0.4%)				1(0.1%)	
Vasculitis			1(0.1%)		2(0.2%)	
Vasospasm	1(0.4%)				1(0.1%)	

More than 50% of patients in the three groups had constipation (53.7%, 56.7%, and 53.8% in TCCU 320 mg/m², TCCU 280 mg/m² and Non-TCCU, respectively) and / or fatigue (54.0%, 48.3%, and 55.0% in TCCU 320 mg/m², TCCU 280 mg/m² and Non-TCCU, respectively).

Grade 3/4 severity was recorded in more than 5% of TCCU patients for febrile neutropenia (TCCU 320 mg/m²: 7.0%; TCCU 280 mg/m²: 6.2%), constipation (TCCU 320 mg/m: 13.2%; TCCU 280 mg/m²: 18.5%), nausea (TCCU 320 mg/m²: 1.5%, TCCU 280 mg/m²: 5.1%), and fatigue (TCCU 320 mg/m²: 14.0%, TCCU 280 mg/m²: 15.7%). In the Non-TCCU group, Grade 3/4 febrile neutropenia was reported in 4.4% of patients, constipation in 10% of patients, nausea in 2.9% of patients and fatigue in 11.8% of patients.

In the TCCU patients, the incidence of AEs observed at 280 mg/m² was generally either equal or superior to that observed at 320 mg/m² reflecting the poorer clinical status of the population treated in this group. However, toxicity remained acceptable and manageable in both groups.

Severe constipation occurred in 15.3% of treated patients. Constipation is reversible and not cumulative. In light of this, the sponsor recommends that 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 once a day in the morning before breakfast from Day 1 to Day 7. In case of Grade 2 constipation for more than 5 days or Grade≥ 3 of any duration, the dose of vinflunine should be adjusted.

The sponsor also recommends dose adjustment in cases 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).

In relation to cardiac safety, QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhythmias although no ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increased proarrhythmic risk (for example, congestive heart failure, known history of QT interval prolongation, hypokalaemia). The concomitant use of two or more QT/QTc interval prolonging drugs is not recommended.

The sponsor also recommended that special attention should be paid when vinflunine is administered to patients with prior history of myocardial infarction/ischaemia or angina pectoris. Ischaemic cardiac events may occur, in particular in patients who have underlying cardiac disease. Patients receiving vinflunine 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.

Serious adverse events and deaths

The incidence of serious adverse events (SAEs) increased across TCCU studies and is correlated to the worsening of patient characteristics [VFL 202 (49.0%) < CA001 (51.0%) < VFL 302 (61.7%)]. In the pivotal study (VFL 302), the difference of SAE incidence is 14.7 % between patients who received chemotherapy (61.7%) and patients included in the BSC arm (47.0%). Table 42 summarises SAEs reported with vinflunine.

Table 42: Serious adverse events, 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)

Related SAEs decrease for gastrointestinal disorders, general disorders and administration site conditions SOCs but remain similar in TCCU versus Non-TCCU groups. Related SAEs are summarised in Table 43.

Table 43: Study treatment related serious adverse events by SOC and by PT (TCCU and Non-TCCU patients)

Studies	VFL TCCU			VFL Non-TCCU
	320	280	VFL ALL	Non-TCCU
	272	178	450	753
SYSTEM ORGAN / PREFERRED TERM				
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**34 (12.5)**	**25 (14.0)**	**59 (13.1)**	**73 (9.7)**
Anaemia	9 (3.3)	9 (5.1)	18 (4.0)	14 (1.9)
Febrile neutropenia	15 (5.5)	9 (5.1)	24 (5.3)	17 (2.3)
Leucopenia	5 (1.8)	2 (1.1)	7 (1.6)	6 (0.8)
Neutropenia	14 (5.1)	9 (5.1)	23 (5.1)	47 (6.2)
Thrombocytopenia	1 (0.4)	2 (1.1)	3 (0.7)	5 (0.7)
CARDIAC DISORDERS	**3 (1.1)**	**1 (0.6)**	**4 (0.9)**	**7 (0.9)**
EYE DISORDERS	**0**	**2 (1.1)**	**2 (0.4)**	**0**
GASTROINTESTINAL DISORDERS	**35 (12.9)**	**34 (19.1)**	**69 (15.3)**	**114 (15.1)**
Abdominal pain	8 (2.9)	9 (5.1)	17 (3.8)	43 (5.7)
Constipation	19 (7.0)	16 (9.0)	35 (7.8)	65 (8.6)
Diarrhoea	2 (0.7)	3 (1.7)	5 (1.1)	6 (0.8)
Dysphagia	1 (0.4)	2 (1.1)	3 (0.7)	3 (0.4)
Ileus	3 (1.1)	7 (3.9)	10 (2.2)	14 (1.9)
Nausea	4 (1.5)	3 (1.7)	7 (1.6)	18 (2.4)
Stomatitis	2 (0.7)	2 (1.1)	4 (0.9)	9 (1.2)
Vomiting	5 (1.8)	8 (4.5)	13 (2.9)	34 (4.5)

Studies	VFL TCCU			VFL Non-TCCU
	320	280	VFL ALL	Non-TCCU
	272	178	450	753
SYSTEM ORGAN / PREFERRED TERM				
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**25 (9.2)**	**16 (9.0)**	**41 (9.1)**	**66 (8.8)**
Asthenia	4 (1.5)	1 (0.6)	5 (1.1)	10 (1.3)
Chest pain	2 (0.7)	0	2 (0.4)	13 (1.7)
Chills	3 (1.1)	1 (0.6)	4 (0.9)	5 (0.7)
Condition aggravated	4 (1.5)	2 (1.1)	6 (1.3)	9 (1.2)
Fatigue	10 (3.7)	4 (2.2)	14 (3.1)	8 (1.1)
Pyrexia	4 (1.5)	5 (2.8)	9 (2.0)	19 (2.5)
INFECTIONS AND INFESTATIONS	**12 (4.4)**	**10 (5.6)**	**22 (4.9)**	**30 (4.0)**
Neutropenic infection	4 (1.5)	5 (2.8)	9 (2.0)	8 (1.1)
Pneumonia	3 (1.1)	1 (0.6)	4 (0.9)	1 (0.1)
INVESTIGATIONS	**3 (1.1)**	**2 (1.1)**	**5 (1.1)**	**9 (1.2)**
METABOLISM AND NUTRITION DISORDERS	**11 (4.0)**	**6 (3.4)**	**17 (3.8)**	**22 (2.9)**
Anorexia	4 (1.5)	2 (1.1)	6 (1.3)	11 (1.5)
Dehydration	5 (1.8)	1 (0.6)	6 (1.3)	9 (1.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**2 (0.7)**	**0**	**2 (0.4)**	**32 (4.2)**
Arthralgia	0	0	0	10 (1.3)
Myalgia	1 (0.4)	0	1 (0.2)	24 (3.2)
NERVOUS SYSTEM DISORDERS	**7 (2.6)**	**2 (1.1)**	**9 (2.0)**	**5 (0.7)**
Headache	3 (1.1)	0	3 (0.7)	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**3 (1.1)**	**3 (1.7)**	**6 (1.3)**	**19 (2.5)**
Dyspnoea	1 (0.4)	0	1 (0.2)	13 (1.7)

SYSTEM ORGAN / PREFERRED TERM				
Pulmonary embolism	0	2 (1.1)	2 (0.4)	0
VASCULAR DISORDERS	**6 (2.2)**	**5 (2.8)**	**11 (2.4)**	**11 (1.5)**
Hypertension	3 (1.1)	2 (1.1)	5 (1.1)	2 (0.3)

Deaths

One hundred and seven patients (8.9%) died within 30 days following the last VFL infusion. The rates of deaths within the 30 days are 7.0 %, 14.6% and 8.2% in the TCCU 320 mg/m², TCCU 280 mg/m² and Non-TCCU patients, respectively. Considering all TCCU patients, the rate of death within 30 days was 10.0%.

In the TCCU population, the incidence of death in the 280 mg/m² group was two-fold higher than in the 320 mg/m² group (14.6% versus 7.0%) which is consistent with the characteristics of patients in each group at inclusion.

The majority of deaths occurring within the 30 days following the last study drug administration were due to disease progression (TCCU: 4.4% and Non-TCCU 5.2%). A total of 48 out of 1203 patients (4.0%) died due to other reasons than progression. This represents 44.9% (48/107) of the total of deaths. Study treatment related deaths (6 in TCCU patients and 6 in Non- TCCU patients) represented 11.2% (12/107) of the total of deaths and accounted for 1% of the whole population deaths (12 out of 1203 patients) (see Table 44).

The following 5 tables (Table 44, Table 45, Table 46, Table 47, and Table 48) summarise the reasons for death of all the patients included in the safety analyses. In the pivotal study (VFL 302), 29 out of 117 patients (24.8%) included in the BSC arm died within 30 days of the last visit. The rate of death in the BSC arm is higher than the rate of death in the VFL+BSC arm (24.8% versus 11.7%, respectively).

Table 44: 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 45: 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 46: Summary description of study drug related adverse events leading to death in TCCU and Non TCCU patients

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

* In study CA001 group 320 i the database, this death is tabulated in 2 places with 2 different causalities (possible or not related). The related causality was considered.

Table 47: Summary description of deaths within 30 days after the last administration for reasons other than progression or VFL-related AEs (TCCU patients)

Study number	Most Probable cause of death	Time of death
VFL 202 320 mg/m² CSR L00070 IN 202 see file	Pneumonitis	Cycle 2 Day 28
	Suspected pulmonary embolism	Cycle 1 Day 9
CA 001 280 mg/m² CSR CA183001 see file	Unknown	Cycle 4 Day 29
	Pulmonary embolism	Cycle 9 Day 9
VFL 302 320 mg/m² CSR L00070 IN 302 see file	Hematemesis	Cycle 1 Day 21
	Bleeding from upper gastrointestinal tract	Cycle 5 Day 9
	Gastrointestinal bleeding	Cycle 2 Day 6
	Unknown	Cycle 2 Day 18
	Cardiac pulmonary failure	Cycle 2 Day 7
VFL 302 280 mg/m² CSR L00070 IN 302 see file	Deterioration of general condition	Cycle 2 Day 9
	Sepsis	Cycle 2 Day 25
	Renal failure	Cycle 1 Day 14
	Pulmonary edema	Cycle 1 Day 9
	Unknown	Cycle 1 Day 8
	Intestinal subocclusion	Cycle 7 Day 21
	Coma	Cycle 3 Day 18
	Acute cardiac pulmonary failure	Cycle 2 Day 13
	Sudden death - Unknown	Cycle 1 Day 23
	Depression	Cycle 1 Day 11

Table 48: Summary description of deaths within 30 days after the last administration for reasons other than progression or related VFL-AEs (VFL Non-TCCU patients)

Study number	Most probable cause of death	Time of death
VFL 201 CSR L00070 IN 201 see file	Pulmonary embolism	Cycle 1 Day 17
VFL 203 CSR L00070 IN 203 see file	Pulmonary embolism	Cycle 1 Day 8
	Lung artery embolism	Cycle 8 Day 25
VFL 204 CSR L00070 IN 204 see file	Cerebro-vascular accident	Cycle 2 Day 10
VFL 208 CSR L00070 IN 208 see file	Pulmonary embolism	Cycle 6 Day 17
VFL 209 CSR L00070 IN 209 see file	Unknown	Cycle 2 Day 20
VFL 301 CSR L00070 IN 301 see file	Hematemesis	Cycle 1 Day 11
	Budd Chiari syndrome	Cycle 3 Day 30
	Pulmonary embolism	Cycle 2 Day 15
	Completed Suicide	Cycle 1 Day 9
	Pulmonary embolism	Cycle 3 Day 31
	Sudden death (unknown)	Cycle 1 Day 7
	Pulmonary oedema	Cycle 1 Day 14
	Acute pulmonary oedema	Cycle 1 Day 1
	Pulmonary embolism	Cycle 1 Day 7
	Pulmonary embolism	Cycle 1 Day 25
	Myocardial infarction	Cycle 3 Day 11

In the TCCU patients, 4 out of the 6 study drug related deaths occurred in patients in the 320 mg/m² group. These events were observed after Cycle 3 in one patient, after Cycle 4 and after the fifth administration in the other 2 patients. Two adverse events were in relation to myelosuppression (pancytopaenia, febrile neutropenia), one in relation to septicaemia and one in relation to a cardio-pulmonary arrest. Two additional TCCU patients who died on study are reported in the 280 mg/m² subset of patients; again, bone marrow depletion was associated with infection and was responsible for one of these 2 SAEs, while the unique case of lethal myocardial infarction was reported in the second patient. When Non-TCCU patients are considered, 4 out of the 6 deaths due to study medication related AEs were the consequence of severe infection.

Laboratory findings

Haemoglobin

Haemoglobin worst grade per patient is summarised in Table 49 below.

Table 49: Worst grade of haemoglobin by patients and cycles

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose mg/m²	320	320	280	All	320	280	All	320	280	All	320
Patients											
No. of patients	51	84	64	148	136	110	246	271	174	445	743
Any grade (%)	46 (90.2)	75 (89.3)	63 (98.4)	138 (93.2)	125 (91.9)	104 (94.5)	229 (93.1)	246 (90.8)	167 (96.0)	413 (92.8)	607 (81.7)
Grade 3/4 (%)	7 (13.7)	11 (13.1)	12 (18.8)	23 (15.5)	22 (16.2)	25 (22.7)	47 (19.1)	40 (14.8)	37 (21.3)	77 (17.3)	47 (6.3)
Grade 4 (%)	0	0	1 (1.6)	1 (0.7)	5 (3.7)	6 (5.5)	11 (4.5)	5 (1.8)	7 (4.0)	12 (2.7)	5 (0.7)
Cycles											
No. of cycle	196	353	207	560	633	397	1030	1182	604	1786	2756
Any grade (%)	169 (86.2)	292 (82.7)	192 (92.8)	484(86.4)	462 (73.0)	334 (84.1)	796 (77.3)	923 (78.1)	526 (87.1)	1449 (81.1)	1818 (66.0)
Grade 3/4 (%)	10 (5.1)	16 (4.5)	13 (6.3)	29 (5.2)	34 (5.4)	33 (8.3)	67 (6.5)	60 (5.1)	46 (7.6)	106 (5.9)	52 (1.9)
Grade 4 (%)	0	0	1 (0.5)	1 (0.2)	6 (0.9)	7 (1.8)	13 (1.3)	6 (0.5)	8 (1.3)	14 (0.8)	5 (0.2)

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. It is noteworthy that the 2/3 of

patients (61.3%) included in the BSC arm of the Phase III trial (VFL 302) also experienced anaemia. Forty seven percent (568/1203) of patients treated with VFL presented with anaemia at baseline. During the treatment period, severe anaemia (Grade 3, haemoglobin e 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 treated at 320 mg/m² and 7 cases (4.0%) in the TCCU patients treated at 280 mg/m². Seven percent (6.8%) of the patients had no anaemia at baseline but experienced Grade 3/4 anaemia as the worst grade during treatment. Among patients presenting with Grade 1/2 at baseline, anaemia worsened to reach Grade 3/4 events in 27.2% of patients during treatment. 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.

Leucocytes

A total of 120 (44.3%) of the TCCU patients in the 320 mg/m² group and 81 (46.6%) of the TCCU patients in the 280 mg/m² group experienced Grade 3/4 leucopaenia during vinflunine treatment. In Non-TCCU patients the incidence of Grade 3/4 leucopaenia was lower (30.8%). Among the patients treated at the recommended dose of 320 mg/m², the median nadir (the lowest point) of leucocytes at cycle 1 was established at 2.3 x 10^9 /L (range [0.2 x 10^9 /L, 5 x 10^9 /L]) at the 7.5 day (range [5, 8]) of vinflunine infusion). Worst grade of leucopaenia is summarised in Table 50 below.

Table 50: Worst grade of leucopaenia by patient and cycles

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose mg/m²	320	320	280	All	320	280	All	320	280	All	320
Patients											
No. of patients	51	84	64	148	136	110	246	271	174	445	743
Any grade (%)	43 (84.3)	76 (90.5)	55 (85.9)	131 (88.5)	113 (83.1)	89 (80.9)	202 (82.1)	232 (85.6)	144 (82.8)	376 (84.5)	533 (71.7)
Grade 3/4 (%)	23 (45.1)	41 (48.8)	32 (50.0)	73 (49.3)	56 (41.2)	49 (44.5)	105 (42.7)	120 (44.3)	81 (46.6)	201 (45.2)	229 (30.8)
Grade 4 (%)	9 (17.6)	10 (11.9)	14 (21.9)	24 (16.2)	23 (16.9)	21 (19.1)	44 (17.9)	42 (15.5)	35 (20.1)	77 (17.3)	70 (9.4)
Cycles											
No. of cycles	196	353	207	560	633	397	1030	1182	604	1786	2756
Any grade (%)	152 (77.6)	252 (71.4)	132 (63.8)	384 (68.6)	369 (58.3)	247 (62.2)	616 (59.8)	773 (65.4)	379 (62.7)	1152 (64.5)	1502 (54.5)
Grade 3/4 (%)	53 (27.0)	81 (22.9)	59 (28.5)	140 (25.0)	89 (14.1)	77 (19.4)	166 (16.1)	223 (18.9)	136 (22.5)	359 (20.1)	364 (13.2)
Grade 4 (%)	12 (6.1)	14 (4.0)	21 (10.1)	35 (6.3)	29 (4.6)	27 (6.8)	56 (5.4)	55 (4.7)	48 (7.9)	103 (5.8)	84 (3.0)

Neutrophils

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 resulted in 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. 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, for example septic shock was reported in 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, one in an ovarian cancer patient and two in TCCU patients. 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 white blood cell (WBC) counts were conducted twice every week. Worst grade of neutrophils summarised in Table 51 below.

Table 51: Worst grade of neutrophils by patient and cycles

	VFL 202	CA 001			VFL 302			VFL TCCU			Non-TCCU
Dose mg/m²	320	320	280	All	320	280	All	320	280	All	320
Patients											
No. of patients	51	84	64	148	136	110	246	271	174	445	743
Any grade (%)	42 (82.4)	68 (81.0)	54 (84.4)	122 (82.4)	112 (82.4)	78 (70.9)	190 (77.2)	222 (81.9)	132 (75.9)	354 (79.6)	528 (71.1)
Grade 3/4 (%)	34 (66.7)	49 (58.3)	37 (57.8)	86 (58.1)	72 (52.9)	51 (46.4)	123 (50.0)	155 (57.2)	88 (50.6)	243 (54.6)	354 (47.6)
Grade 4 (%)	18 (35.3)	35 (41.7)	25 (39.1)	60 (40.5)	50 (36.8)	32 (29.1)	82 (33.3)	103 (38.0)	57 (32.8)	160 (36.0)	191 (25.7)
Cycles											
No. of cycles	196	353	207	560	633	397	1030	1182	604	1786	2756
Any grade (%)	144 (73.5)	223 (63.2)	121 (58.5)	344 (61.4)	359 (56.7)	205 (51.6)	564 (54.8)	726 (61.4)	326 (54.0)	1052 (58.9)	1504 (54.6)
Grade 3/4 (%)	82 (41.8)	109 (30.9)	67 (32.4)	176 (31.4)	151 (23.9)	95 (23.9)	246 (23.9)	342 (28.9)	162 (26.8)	504 (28.2)	720 (26.1)
Grade 4 (%)	39 (19.9)	55 (15.6)	41 (19.8)	96 (17.1)	76 (12.0)	51 (12.8)	127 (12.3)	170 (14.4)	92 (15.2)	262 (14.7)	276 (10.0)

Platelets

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

Liver function-Bilirubin

Worst grade of bilirubin per patient is summarised in Table 52 below.

Table 52: 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

Overall, the incidence of Grades 3 and 4 toxicity was low and there was no relevant difference between groups: 1.9% of TCCU (320 mg/m²) patients, 2.4% of TCCU (280 mg/m²) patients and 0.8% of Non-TCCU patients. For alkaline phosphatase, the picture was very similar; 18 patients (4.1%) experienced Grade 3 or 4 levels. Grade 3 and Grade 4 levels of AST and ALT were very infrequently observed (3 cases (0.7), irrespective of 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 (may be 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. No worsening of serum creatinine levels was observed while 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 was observed when considering the Grade 3/4 creatininaemia which remained low (TCCU: 1.1%, Non-TCCU: 0.4%).

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 patients with 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 was slightly higher (13.7%) in TCCU patients treated at 280 mg/m². The incidence of hyponatraemia was 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 conducted. This study was designed to determine the recommended dose of vinflunine and to investigate the pharmacokinetics and tolerability of IV vinflunine in cancer patients with chronic liver dysfunction. This study investigated whether there is a relationship between drug exposure and adverse events or biological modifications. It also assessed the antitumor activity.

Three groups were scheduled according to the liver dysfunction to receive 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 of tolerance:

Group 1: Mild chronic liver dysfunction:

Prothrombin Time ≥ 70% normal (N) and, upper normal limit (ULN) < bilirubin ≤ 1.5 x ULN and/or 1.5 x ULN < transaminases ≤ 2.5 x ULN and/or ULN < GGT ≤ 5 ULN

Group 2: Moderate chronic liver dysfunction:

Patient with a Child-Pugh Grade A cirrhosis or

Prothrombin Time ≥ 60% N and 1.5 x ULN< bilirubin ≤ 3 x ULN and transaminases > ULN and/or GGT > 5 x ULN

Group 3: Severe chronic liver dysfunction

Patient with a Child-Pugh Grade B cirrhosis, or

Prothrombin Time ≥ 50% N and 1.5 x ULN< bilirubin >3 x ULN and transaminases > ULN and GGT > ULN.

Both vinflunine and its main metabolite, 4-Odeacetylvinflunine (DVFL) PK parameters showed no significant differences between patients with liver impairment and control groups. However, the safety data from the Phase I study indicated that the dose of vinflunine needed to be adjusted to 250mg/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, and this should be reflected in the Product Information (PI).

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 there were 6 evaluable patients; one experienced neutropenia and thrombocytopenia and five patients experienced anaemia and leucopaenia. One episode of febrile neutropenia was recorded and two patients 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, 9 patients treated for a total of 37 cycles had anaemia which was of Grade 3 in two patients. Grade 3 and 4 neutropenia were observed in four patients and Grade 3 thrombocytopenia was seen in two patients. In relation to 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 melaena were observed. Table 53 summarises dose limiting toxicities at Cycle 1 by group of liver impairment and by vinflunine dose.

Table 53: Dose limiting toxicities at Cycle 1 by group of liver impairment and by vinflunine dose

Group	Vinflunine dose at cycle 1	Dose limiting toxicity at cycle 1
1 - mild liver dysfunction	320 mg/m²	GGT increase > 25%
		GGT increase > 25% and grade 3 fatigue
2 - moderate liver dysfunction	320 mg/m²	GGT increase > 25% and SGPT increase > 50%
		Grade 3 constipation and hypertension, grade 4 fatigue
		Bilirubin increase > 25%, GGT increase > 25%, SGOT increase > 50%, grade 3 constipation and grade 3 neutropenic infection
	250 mg/m²	Bilirubin increase > 25%, Febrile Neutropenia
		GGT increase > 25% and bilirubin increase > 25%
3 - severe liver dysfunction	250 mg/m²	GGT increase > 25%
		GGT increase > 25% and bilirubin increase > 25%
		Grade 4 neutropenia and grade 3 constipation
	200 mg/m²	Bilirubin increase > 25%
		GGT increase > 25% and SGPT increase > 50%

On the basis of these data the sponsor is recommending the following doses for the first cycle of vinflunine.

- In patients with mild liver dysfunction the recommended dose of vinflunine is 320 mg/m² given once 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 vinflunine is 200 mg/m², once every 3 weeks.

Renal impairment

There is an ongoing PK study of IV vinflunine in cancer patients with renal impairment. Results from the interim analysis from this Phase I study were provided.

The primary objective is to study the effect of renal impairment on the pharmacokinetics of vinflunine and DVFL in adult cancer patients with varying degrees of renal dysfunction and to propose a dose adjustment, when required, in order to target the area under the curve (AUC) corresponding to the recommended dose. The secondary objectives are to assess the

safety of vinflunine in adult cancer patients with varying degrees of renal dysfunction and, to determine any relationship between drug exposure and adverse events or biological modifications. This is an open-label, non-randomised, multicentre pharmacokinetic Phase I study.

Patients are stratified by severity of renal impairment according to the value of creatinine clearance (CLcr) at baseline, calculated using the Cockcroft and Gault formula. In order to reduce variability in the measurement of serum creatinine, CLcr is calculated using the values of serum creatinine assayed by a central laboratory. Renal impairment groups are defined as follows:

• Group 1 moderate renal impairment: Creatinine clearance (calculated) from≥ 40 mL/min to ≤ 60 mL/min.

• Group 2 severe renal impairment: Creatinine clearance (calculated) from≥ 20 mL/min to < 40 mL/min.

Interim results showed that Clcr of vinflunine decreased in patients with renal impairment. This decrease was of approximately 16% in patients with moderate renal impairment and of approximately 30% in patients with severe renal impairment (Creatinine clearance (calculated) from ≥20 ml/min to ≤40 ml/min). Therefore, the sponsor has recommended that the vinflunine dose should be reduced in patients with moderate or severe renal impairment.

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 was commenced in January 2005 and is still ongoing. No results are available.

Paediatric population

No studies have been submitted in this specific population.

Immunological events

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

Safety related to drug-drug interactions and other interactions

Combining strong CYP3A4 inhibitors represents a real risk of VFL overexposure if the recommended dose is administered. Such combined treatment should be avoided when possible. Studies indicate that strong inhibitors of CYP3A4 such as itraconazole, ritonavir and ketoconazole are likely to inhibit the metabolism of vinflunine.

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 AUC_{inf} of vinflunine, a 31% increase in dose-normalised $AUC_{(0\text{-}96h)}$ of DVFL and a 49% increase in dose-normalized $AUC_{(0\text{-}168h)}$ of DVFL. Co-administration of ketoconazole at 400 mg per day for 8 days did not affect the dose-normalised C_{max} of a 20 minute IV infusion of vinflunine but increased the dose-normalised C_{max} for DVFL by 17%. The maximum tolerated dose of vinflunine is defined as 160 mg/m² when co-administered with 400 mg of ketoconazole.

In vitro and *in vivo* studies have been conducted to assess the effects of vinflunine when used in combination with chemotherapeutic agents such as cisplatin, carboplatin, gemcitabine, doxorubicin, pegylated doxorubicin and capecitabine. 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.

Taxanes such as paclitaxel and docetaxel also inhibit metabolism of vinflunine to some extent, however not as markedly.

Discontinuation due to adverse events

A total of 56 vinflunine treated TCCU patients (12.7%) stopped their treatment due to study treatment related adverse events. This can be compared to 10.8% of Non-TCCU patients. Of note in the BSC arm of the pivotal study was that the proportion of patient withdrawals due to AE was 6.0%. This can be compared to 20% in the VFL+BSC arm of which 12.2% were treatment related. Table 54 summarises study withdrawal in relation to safety.

Table 54: Study withdrawal in relation with safety, 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
No. of patients	51	80*	66	146*	133*	112	245*	264*	178	442*	753
Withdrawal due to AE	8 (15.7)	12 (15.0)	8 (12.1)	20 (13.7)	22 (16.5)	27 (24.1)	49 (20.0)	42 (15.9)	35 (19.7)	77 (17.4)	99 (13.1)
Withdrawal due to treatment related AE	7 (13.7)	11(13.8)	8 (12.1)	19 (13.0)	14 (10.5)	16 (14.3)	30 (12.2)	32 (12.1)	24 (13.5)	56 (12.7)	81 (10.8)
Withdrawal due to unrelated AE	1 (2.0)	1 (1.3)	0	1 (0.7)	8 (6.0)	11 (9.8)	19 (7.8)	10 (3.8)	11 (6.2)	21 (4.8)	18 (2.4)

Table 4.2.5.1-5. Discrepancies between withdrawal due to AEs in Table 27 and Table 28 for some patients is explained by the fact that investigators considered the withdrawal not due to AE. In the AE form AEs were mentioned as leading to discontinuation.; *: excluding 8 patients under treatment at the cut off date (5 patients in CA 001 and 3 patients in VFL 302)

All related adverse events leading to study drug discontinuation are listed below in Table 55 by preferred term (excluding patients who discontinued due to disease progression). The AEs leading to treatment discontinuation are generally the same as those seen in the overall safety profile of VFL and the rate is similar in both dose groups (320 mg/m² versus 280 mg/m²). Of note is that one patient discontinued due to more than one AE. In 12 out of 220 TCCU patients who received at least 4 cycles the reason for discontinuation was mainly due to fatigue/asthenia, (12/31 AEs).

Table 55: Adverse events (related to vinflunine) leading to treatment discontinuation, TCCU and Non-TCCU patients

	VFL TCCU N (%)			Non TCCU N (%)
Doses (mg/m²)	320	280	All	320
No. of patients	264*	178	442*	753
ANY ADVERSE EVENT	36 (13.6%)	25 (14.0%)	61 (13.8%)	81 (10.8%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6 (2.3%)	4 (2.2%)	10 (2.3%)	5 (0.7%)
Anaemia	1 (0.4%)	1 (0.6%)	2 (0.5%)	0
Febrile neutropenia	1 (0.4%)	1 (0.6%)	2 (0.5%)	3 (0.4%)
Leukopenia	0	1 (0.6%)	1 (0.2%)	0
Neutropenia	3 (1.1%)	2 (1.1%)	5 (1.1%)	2 (0.3%)
Pancytopenia	1 (0.4%)	0	1 (0.2%)	0
Thrombocytopenia	0	0	0	1 (0.1%)
CARDIAC DISORDERS	3 (1.1%)	0	3 (0.7%)	2 (0.3%)
Cardio-respiratory arrest	1 (0.4%)	0	1 (0.2%)	0
Myocardial ischaemia	2 (0.8%)	0	2 (0.5%)	2 (0.3%)

Table 55 continued.

ENDOCRINE DISORDERS	0	0	0	1 (0.1%)
Inappropriate antidiuretic hormone secretion	0	0	0	1 (0.1%)
GASTROINTESTINAL DISORDERS	10 (3.8%)	8 (4.5%)	18 (4.1%)	24 (3.2%)
Abdominal pain	0	1 (0.6%)	1 (0.2%)	8 (1.1%)
Anal fistula	0	0	0	1 (0.1%)
Constipation	6 (2.3%)	4 (2.2%)	10 (2.3%)	11 (1.5%)
Diarrhoea	1 (0.4%)	1 (0.6%)	2 (0.5%)	0
Dry mouth	0	0	0	1 (0.1%)
Ileus	1 (0.4%)	1 (0.6%)	2 (0.5%)	4 (0.5%)
Ileus paralytic	1 (0.4%)	0	1 (0.2%)	0
Nausea	0	1 (0.6%)	1 (0.2%)	0
Pancreatitis	1 (0.4%)	0	1 (0.2%)	0
Stomatitis	0	1 (0.6%)	1 (0.2%)	3 (0.4%)
Vomiting	1 (0.4%)	1 (0.6%)	2 (0.5%)	2 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (5.3%)	8 (4.5%)	22 (5.0%)	23 (3.1%)
Asthenia	0	1 (0.6%)	1 (0.2%)	1 (0.1%)
Chest pain	0	0	0	1 (0.1%)
Chills	1 (0.4%)	0	1 (0.2%)	0
Condition aggravated	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Fatigue	12 (4.5%)	7 (3.9%)	19 (4.3%)	15 (2.0%)
Infusion site reaction	0	0	0	4 (0.5%)
Injection site reaction	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
IMMUNE SYSTEM DISORDERS	0	0	0	2 (0.3%)

	VFL TCCU N (%)			Non TCCU N (%)
Doses (mg/m²)	320	280	All	320
No. of patients	264*	178	442*	753
Hypersensitivity	0	0	0	2 (0.3%)
INFECTIONS AND INFESTATIONS	4 (1.5%)	2 (1.1%)	6 (1.4%)	8 (1.1%)
Abscess	1 (0.4%)	0	1 (0.2%)	0
Cellulitis	0	0	0	1 (0.1%)
Infection	0	0	0	2 (0.3%)
Neutropenic infection	0	2 (1.1%)	2 (0.5%)	2 (0.3%)
Neutropenic sepsis	0	0	0	1 (0.1%)
Pneumonia	2 (0.8%)	0	2 (0.5%)	0
Sepsis	1 (0.4%)	0	1 (0.2%)	0
Septic shock	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Tonsillitis	0	0	0	1 (0.1%)
INVESTIGATIONS	0	0	0	5 (0.7%)
Alanine aminotransferase increased	0	0	0	1 (0.1%)
Aspartate aminotransferase increased	0	0	0	1 (0.1%)
Electrocardiogram T wave abnormal	0	0	0	1 (0.1%)
Gamma-glutamyltransferase increased	0	0	0	3 (0.4%)
METABOLISM AND NUTRITION DISORDERS	2 (0.8%)	0	2 (0.5%)	2 (0.3%)
Anorexia	2 (0.8%)	0	2 (0.5%)	1 (0.1%)
Dehydration	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	3 (1.7%)	3 (0.7%)	10 (1.3%)
Arthralgia	0	1 (0.6%)	1 (0.2%)	3 (0.4%)
Back pain	0	0	0	1 (0.1%)
Bone pain	0	0	0	3 (0.4%)

Table 55 continued.

Groin pain	0	1 (0.6%)	1 (0.2%)	0
Muscular weakness	0	1 (0.6%)	1 (0.2%)	0
Myalgia	0	1 (0.6%)	1 (0.2%)	4 (0.5%)
Pain in jaw	0	0	0	2 (0.3%)
NERVOUS SYSTEM DISORDERS	4 (1.5%)	3 (1.7%)	7 (1.6%)	4 (0.5%)
Convulsion	0	1 (0.6%)	1 (0.2%)	0
Dizziness	1 (0.4%)	1 (0.6%)	2 (0.5%)	0
Headache	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Hypoaesthesia	1 (0.4%)	0	1 (0.2%)	0
Neuralgia	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Neuropathy	1 (0.4%)	0	1 (0.2%)	0
Paraesthesia	1 (0.4%)	0	1 (0.2%)	2 (0.3%)
Peripheral sensory neuropathy	1 (0.4%)	1 (0.6%)	2 (0.5%)	0
PSYCHIATRIC DISORDERS	0	0	0	1 (0.1%)
Confusional state	0	0	0	1 (0.1%)
RENAL AND URINARY DISORDERS	0	0	0	1 (0.1%)
Renal tubular necrosis	0	0	0	1 (0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.4%)	3 (1.7%)	4 (0.9%)	3 (0.4%)
Acute respiratory distress syndrome	0	1 (0.6%)	1 (0.2%)	2 (0.3%)
Cryptogenic organising pneumonia	1 (0.4%)	1 (0.6%)	2 (0.5%)	0
Interstitial lung disease	0	0	0	1 (0.1%)
Pulmonary embolism	0	1 (0.6%)	1 (0.2%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.6%)	1 (0.2%)	2 (0.3%)
Rash	0	1 (0.6%)	1 (0.2%)	0
Skin necrosis	0	0	0	1 (0.1%)
Urticaria	0	0	0	1 (0.1%)
VASCULAR DISORDERS	2 (0.8%)	2 (1.1%)	4 (0.9%)	1 (0.1%)
Deep vein thrombosis	1 (0.4%)	0	1 (0.2%)	0
Hypertension	1 (0.4%)	1 (0.6%)	2 (0.5%)	1 (0.1%)
Ischaemia	0	1 (0.6%)	1 (0.2%)	0
Orthostatic hypotension	0	1 (0.6%)	1 (0.2%)	0

Table 4.2.5.1-16; Discrepancies between withdrawal due to AEs in Table 27 and Table 28 is due for some patients by the fact that investigators considered the withdrawal not due to AE. In the AE form AEs were mentioned as leading to discontinuation; *: excluding 8 patients under treatment at the cut off date (5 patients in CA 001 and 3 patients in VFL 302).

Post marketing experience

No post marketing data were submitted for evaluation.

Evaluator's overall conclusions on clinical safety

The overall patient exposure to vinflunine is considered adequate for assessment of safety. 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 and 320 mg/m²) was comparable with slightly higher rates of AEs 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 considered not to be related to the study medication.

The main dose limiting toxicity is neutropenia . Neutropenia and anaemia are familiar AEs for physicians in the field of oncology and it is likely that these problems can be managed by a variety of medical measures such as G-CSF and blood transfusions. In all cases a close monitoring of haematological parameters is required during treatment.

Constipation is common but reversible and non cumulative. When prophylactic treatment with laxative is administered as recommended by the protocol, the rate of constipation is reduced. Therefore the use of laxatives is recommended from Day 1 to Day 5 or Day 7 of VFL administration to alleviate the risk of constipation and should certainly be used in patients at risk of constipation (for example patients with peritoneal carcinomas, abdominal masses and prior extensive abdominal surgery).

Particular attention should be paid to patients presenting with a history of cardiac ischemic disease or angina pectoris. Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischaemia were experienced by 0.6% of the patients and most of them had pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and another died due to a cardiopulmonary arrest.

One study was performed in patients with hepatic impairment. 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.

In general, the safety profile of VFL is well characterised, acceptable and manageable by appropriate dose modifications leading to a low rate of discontinuation and treatment related deaths.

List of Questions

During 2010, the TGA began to change the way applications are evaluated. As part of this change, after an initial evaluation, a "List of Questions" to the sponsor is generated.

Safety

1. It should be requested that the sponsor submit data from all ongoing studies as soon as the studies are completed.

Product Information/Consumer Medicine Information (CMI)

2. *Adverse reactions in other indications:* There are discrepancies between the information listed in the PI, the Summary of Clinical Safety and the EU Summary of Product Characteristics (SmPC) in terms of the frequencies of blood and lymphatic disorders, gastrointestinal disorders, cardiovascular disorders and respiratory, thoracic and mediastinal disorders in non TCCU patients. It should be requested that the sponsor comment on the discrepancies, and clarify the source of the data in this section of the PI.

Sponsor's response:

In their pre-ACPM response, the sponsor provided updated versions of the Australian PI and CMI as well as a tabulation of serious unexpected adverse events from postmarketing data and clinical trials.

Clinical Summary and Conclusions

In support of this application for registration of vinflunine the sponsor submitted one Phase III and two Phase II studies that assessed use of vinflunine 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 multicentre open-label, single-arm Phase II clinical trials a total of 202 patients were treated with vinflunine. In the multicentre, 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 Phase III study, Study 302, was appropriately designed and conducted to assess efficacy and safety of vinflunine and it is considered to be the pivotal study.

Efficacy

In Study 302, the median overall survival was 6.9 months for vinflunine + BSC which can be compared to 4.6 months for BSC alone. This 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 for vinflunine + BSC treatment which can be compared to 1.5 months for BSC alone (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 in 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 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 for prognostic factors, the analyses of OS in the subgroups of patients without or with prior cisplatin showed HRs (95% CI) of 0.53 (0.32 – 0.88; p=0.0143) and 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 for prognostic factors, the analyses of PFS in the subgroups of patients without or with prior cisplatin showed HRs (95% CI) of 0.51(0.31 – 0.86; p=0.0111) and 0.63(0.48 – 0.84; p=0.0016), respectively.

Safety

The most frequent treatment-related adverse reactions reported in the patients with transitional cell carcinoma of the urothelium (450 patients treated with vinflunine) were haematological disorders, mainly neutropenia , anaemia, leucopaenia and thrombocytopaenia; 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 neutropaenic 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, musculoskeletal pain, chest pain, chills and oedema.

Grade 3/4 neutropenia was observed in 54.6% of patients. Severe anaemia and thrombocytopenia were less common (17.3 and 4.9%, respectively). Febrile neutropenia, defined as ANC < 1,000/$mm^3$and fever ≥ 38.5°C of unknown origin without clinically microbiologically documented infection (NCI CTC version 2.0), was observed in 6.7% of

patients. Overall 6 patients (1.3% of the treated population) died from infection as a complication occurring during neutropenia .

Constipation is a class effect of the vinca alkaloids: 15.3% of patients experienced severe constipation during treatment with vinflunine.

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

Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischaemia 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 a myocardial infarction and another patient died due to a cardiopulmonary arrest. Few QT interval prolongations have been observed after the administration of vinflunine.

Benefit risk assessment

Benefits

In the whole randomised population of the pivotal Phase III study (VFL 302), the objective of a median survival advantage of two months favouring VFL + BSC was achieved (6.9 months versus 4.6 months); however the result was not statistically significant (p = 0.2868). A pre-specified multivariate analysis performed on the whole randomised population demonstrated that VFL has a statistically significant treatment effect (p = 0.036) on overall survival when prognostic factors (PS, visceral involvement, alkaline phosphates, haemoglobin, pelvic irradiation) are taken into consideration. In this model VFL reduced the risk of death by 23% compared to BSC with a Hazard Ratio of 0.77.

This statistically significant effect of VFL on overall survival was observed again in the eligible population (357 patients) who corresponds more closely to patients with TCCU who would be considered for active therapy. In the eligible population the objective of achieving a 2 month difference in OS was met (6.9 months versus 4.3 months) and the risk of death was reduced by 22% with an HR of 0.78; this difference is statistically significant (p = 0.0403).

Secondary efficacy endpoints of progression free survival, overall response rate and disease control rate, which are of particular interest in this population, were all statistically significant in favour of VFL + BSC.

Overall the clinical development program of VFL in patients after failure of a prior platinum-containing regimen for advanced/metastatic TCCU has shown consistency in producing a significant and meaningful benefit over a range of efficacy parameters: response rate, disease control rates, progression free survival and overall survival.

Risks

The main dose limiting toxicity associated with vinflunine is neutropenia . Neutropenia and anaemia are common AEs that physicians in the field of oncology monitor and they may be managed by a variety of medical measures such as G-CSF and blood transfusions. In all cases a close monitoring of haematological parameters is required during treatment with vinflunine.

Constipation is common but reversible and non cumulative. When prophylactic treatment with a laxative is administered as recommended by the protocol, the rate of constipation is reduced.

Cardiac toxicity has been observed during the clinical trial program for vinflunine. Even though the incidence of myocardial infection is low, particular attention should be paid to patients presenting with a history of cardiac ischaemic disease or angina pectoris.

In the population of second line advanced/metastatic TCCU patients refractory to a prior platinum-containing regimen, the safety profile of VFL is acceptable and manageable by appropriate dose modifications leading to a low rate of discontinuation and treatment-related deaths.

In summary VFL has a well-characterised safety profile and is generally well-tolerated by patients in both dosage groups of 280 mg/m² or 320 mg/m². This is particularly important in this setting where all patients had undergone extensive prior therapy (surgery, radiotherapy and polychemotherapy).

Balance

The efficacy results overall support that vinflunine is effective treatment for patients with TCCC. The pivotal study, VFL 302, failed to achieve its primary endpoint, probably 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.

Secondary endpoints all favoured the vinflunine arm, indicating efficacy of the product. In the eligible population, a difference in median survival of about 2 months favouring the VFL+BSC arm was observed (6.9 months versus 4.3 months). A stratified log-rank test showed a survival difference between the two 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.

Patient exposure to vinflunine is considered adequate for safety assessment. The main toxicities of vinflunine were neutropenia , anaemia, constipation and asthenia/fatigue, all these adverse events being class effects of the vinca alkaloids. The main dose limiting toxicity is neutropenia . No cumulative toxicities were apparent in patients with TCCU receiving vinflunine and in general, adverse events associated with vinflunine were transient and manageable.

There is currently no standard therapy in patients with advanced urothelial carcinoma, whose disease has progressed after or during a prior platinum-containing regimen. The clinical evaluator considered that the data presented support the conclusion that vinflunine is effective treatment and results in clinically meaningful activity in this group of patients. The medicine therefore fulfils an unmet clinical need. Efficacy is supported by positive results of vinflunine on a range of parameters including PFS, ORR, DC.

There are a few aspects of the data that raise concerns. There was no difference observed in the pre-specified primary analysis of overall survival for vinflunine compared to best standard of care in the intent-to-treat population, based on the single pivotal study provided. In Study 302, a difference in overall survival was only observed in *post hoc* exploratory analyses, excluding patients from the ITT population. There are potential biases arising from these specific exclusions that have not been entirely addressed. Furthermore, in patients who were adequately pre-treated with cisplatin, vinflunine showed a lower level of activity compared to those treated with non-standard platinum compounds.

Overall however the clinical evaluator believed that the data 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. These patients have few available therapeutic options.

Conclusions

It is considered that 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.

RECOMMENDED CONDITIONS FOR REGISTRATION

On the basis of the data submitted for evaluation it is recommended that this Category 1 application to register a new chemical entity, vinflunine ditartrate, ***should be approved.***

The proposed indication as follows is appropriate:

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

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

The format of the RMP version 1 is generally in accordance with the EU template and the information provided satisfactory. Information on the nonclinical and clinical safety concerns and adverse events (AEs) are consistent with those expected with a vinca alkaloid. The AEs include constipation, anaemia, neutropenia and asthenia. They tended to be more frequent in patients receiving a lower dose of VFL due to poorer pretreatment clinical status and prior radiotherapy.

The following identified and potential risks, and missing information were nominated by the sponsor:

Important identified risks:	Myelosuppression: neutropenia , febrile neutropenia and neutropaenic infection.
	Constipation and ileus.
Important potential risks:	Ischaemic cardiac events.
Missing information:	Reproductive toxicity.
	Patients with severe peripheral neuropathy.
	Off label use.

Routine pharmacovigilance (PhV) and risk minimisation activities are proposed[19].

[19] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

The OPR had a number of concerns with the RMP relating to classification of risks, predicted use in Australia, quantification of AEs, interactions with proarrhythmic drugs, frequency of pharmacological class effects with VFL compared to other vinca alkaloids and information on ongoing and planned studies that contribute to pharmacovigilance through assessment of safety.

The proposed Australian Product Information (PI) and EU Summary of Product Characteristics (SmPC) dated September 2009 were also reviewed. Queries are raised about the placement of information in the PI, the description and numbers of AEs and that the Conditions of the Marketing Authorisation indicate that the marketing authorisation holder has committed in Europe to studies and PhV activities detailed in a revised European RMP.

The sponsor subsequently submitted a revised RMP (version 6) which included:

- Information on the results of the study in elderly patients;
- Neurotoxicity as an identified risk and associated AE data;
- Medication error (intrathecal use) as an important potential risk;
- Pro-arrhythmic drugs in the *Interactions* section;
- Reference to PI additions regarding interactions with pro-arrhythmic drugs;
- Additional advice regarding monitoring of haematological parameters;
- PI modifications regarding precautions for gastrointestinal disorders; and
- Risk minimisation for neurotoxicity, medication errors, reproductive toxicity, patients with peripheral neuropathy and off label use in the paediatric population.

A revised PI was also provided. This includes reference to all concerns identified in the evaluation of RMP version 1 and had the information provided in RMP version 6.

OPR recommendations to the Delegate

It is recommended to the Delegate that in addition to RMP version 6, the sponsor should be required to provide:

- Separate assessment and analysis of the following in PSURS:
  - Reports describing cardiac events; and
  - Reports in the age groups 70-75, 75-80 and ≥ 80years with information on dosage as available.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Javlor is a simple aqueous solution. The application was considered at the 133rd Pharmaceutical Subcommittee meeting (in 2010). All issues were resolved. The quality evaluator supported registration.

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Nonclinical

Vinflunine exposure in animal studies was at or below the proposed clinical exposure due to the high toxicity of the drug. Toxic effects included myelosuppression, liver, neuro-, cardiac and reproductive toxicity. The drug was teratogenic in rats and rabbits. Mutagenicity and clastogenicity were seen in mammalian systems *in vitro* and *in vivo*. There were no carcinogenicity studies. The toxicity was consistent with that of other vinca alkaloids.
The nonclinical evaluator supported registration.

Clinical

Pharmacokinetics

Pharmacokinetic information was derived from several studies in cancer patients. Vinflunine has a large volume of distribution (35 ± 9 L/kg) suggestive of distribution to tissues. Blood clearance is high (about 40 L/h). Metabolism is low and variable (10-40%). The major metabolite, 4-O-deacetylvinflunine (DVFL), was active. DVFL is formed by esterases whereas other metabolites are formed by cytochrome CYP3A4. The terminal half-life of vinflunine is 40 h and that of DVFL 120 h. Elimination occurs in urine and faeces. Pharmacokinetics were linear over the dose range 30 -400 mg/m^2.
In a study of vinflunine IV in cancer patients with varying degrees of liver impairment (n=25), the dose-adjusted AUC and clearance were reasonably constant for both vinflunine and DVFL. A population pharmacokinetic analysis confirmed the lack of a relationship between vinflunine and DVFL clearance and markers of liver impairment. However, dose adjustment is recommended for moderate and severe impairment because of lower tolerated vinflunine doses. Moderate liver impairment corresponded to Child-Pugh A and severe liver impairment to Child-Pugh B. Patients with Child-Pugh A impairment had a maximum tolerated vinflunine dose of 320 mg/m^2 and those with Child-Pugh B impairment, 250 mg/m^2. The recommended doses for Child-Pugh A and B impairment were 250 and 200 mg/m^2, respectively. Patients with Child-Pugh C impairment were not studied.
In a study of vinflunine IV in cancer patients with varying degrees of renal impairment (n=22), vinflunine and DVFL clearance were reduced by a mean 16% in moderate impairment (CrCl 40-60 mL/min) and 30% in severe impairment (CrCl 20-40 mL/min). Therefore, dose adjustment is recommended in moderate and severe renal impairment.

Concomitant ketoconazole, a strong CYP3A4 inhibitor, induced a 30% increase in vinflunine and DVFL exposure. Therefore, concomitant use of vinflunine and strong CYP3A4 inhibitors should be avoided.

Pharmacodynamics

In pharmacodynamic trials, the optimum dose and schedule of administration of vinflunine was determined as 350 mg/m^2 once every 3 weeks. Dose-limiting toxicities were neutropenia, constipation and mucositis. There was a high incidence of myelotoxicity with this dose in early trials and the dose was therefore reduced to 320 mg/m^2. The dose was further reduced to 280 mg/m^2 for patients at high risk of myelosuppression (previous pelvic radiotherapy or performance status ≥ 1) after a retrospective safety analysis of a Phase II trial (VFL 202).

Efficacy

In the pivotal trial (VFL302) conducted globally, patients with advanced or metastatic transitional cell carcinoma (TCC) of the urothelial tract who had progressed on a platinum-based regimen, were randomised 2:1 to vinflunine plus best supportive care (BSC) or BSC alone. ECOG or WHO performance status was required to be 0 or 1. Vinflunine was administered IV over 20 minutes every 3 weeks. The dose was 320 mg/m^2 for patients with PS 0 and no previous pelvic irradiation. For patients with PS 1 or previous pelvic irradiation

the dose was 280 mg/m^2, which was increased to 320 mg/m^2 in the second cycle if there were no haematological toxicities causing treatment delay. The dose was subsequently adjusted according to toxicity. The majority of patients were men (80%) and median age was 64 years (range 35-85). The study was open-label. There was independent assessment of efficacy. Treatment was continued until disease progression or unacceptable toxicity (or 18 weeks in the case of BSC).
Vinflunine did not significantly increase overall survival (the primary endpoint) but significantly increased progression-free survival and partial response (Table 57).
Table 57. Efficacy Results – Phase III Trial (VFL 302) – Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract Second Line (31 May 2007 Cut-Off)

	VFL+BSC	**BSC**	**Difference/Hazard Ratio [95% CI]**
Evaluable Patients	**n=185**	**n=85**	
Overall Response Rate[1] (Complete+Partial) %	8.6 (0+8.6)	0 (0+0)	8.6 [5.0, 13.7]
Intent-to-Treat	**n=253**	**n=117**	
Progression-Free Survival[1] *median months*	3.0	1.5	0.68 [0.54, 0.86]
Overall Survival *median months*	6.9	4.6	0.88 [0.69, 1.10]
Overall Survival (adjusted)[2]			0.77 [0.61, 0.98]
Eligible Patients	**n=249**	**n=108**	
Overall Survival *median months*	6.9	4.3	0.78 [0.61, 0.96]

VFL: Vinflunine, BSC: Best Supportive Care. [1] Independent Review. [2] Cox proportional hazards model.

A marginally statistically significant increase in overall survival of median 2.3 months was achieved in a pre-specified multivariate analysis which adjusted for prognostic factors (PS, visceral involvement, alkaline phosphatase, haemoglobin, pelvic irradiation; see Table 57).

A marginally statistically significant increase in overall survival of median 2.6 months was also achieved in an "eligible patient" analysis which excluded major protocol violators (Table 57).

Two uncontrolled Phase II trials of vinflunine at the same dose and for the same indication as the pivotal trial achieved similar overall survival as the pivotal trial: median survival was 6.6 months in Study VFL 202 (n=51) and 7.9 months in trial CA 001 (n=151). The first six patients in trial VFL 202 received a dose of 350 mg/m^2. However, excessive myelosuppression was observed at this dose and the patients were excluded from the efficacy analysis.

Safety

A pooled summary of safety from vinflunine trials was presented. There were 450 patients

with TCC of the urinary tract (from Studies VFL 302, VFL 202 and CA001) and 753 with other cancers. In TCC of the urinary tract, the median number of cycles of vinflunine was 3 (range 1-21). In other cancers, the median number of cycles was 3 (range 1-20).
In TCC of the urinary tract, the most common adverse reactions were anaemia (93%), Leukopenia (85%), neutropenia (80%), constipation (55%), thrombocytopenia (54%), fatigue (52%), nausea (41%), anorexia (34%), alopecia (29%), vomiting (27%) and stomatitis (27%) which are class effects of the vinca alkaloids. These reactions were severe in many patients: anaemia (18%), Leukopenia (45%), neutropenia (55%), fatigue (15%), constipation (15%), thrombocytopenia (5%), nausea (3%), anorexia (3%), vomiting (3%), stomatitis (3%).
There were six deaths (1%) related to vinflunine in patients with TCC of the urinary tract. Four deaths were due to myelosuppression and consequent infection and two due to cardiac disorders – CE, pp.72-5. Serious events included febrile neutropenia (7%), infection with severe neutropenia (5%), arrhythmia (2%), myocardial infarction or ischaemia (1%) and peripheral sensory neuropathy (11%). Not all were considered treatment-related. Dose reduction due to adverse reactions occurred in one-third of patients.
In other cancers (n=753), the safety profile of vinflunine was similar to that in TCC of the urinary tract.
The Safety Specification (*Risk Management Plan* pp.6-35) conformed with the clinical and nonclinical experience.

The clinical evaluator supported registration.

Risk Management Plan (RMP)

The RMP was generally acceptable after an update in response to the *RMP Evaluation*. The update includes recommendations for dose reduction in the elderly based on the final report of a pharmacokinetic study in the elderly submitted in response to the *RMP Evaluation*. For patients 75-80 years, the recommended vinflunine dose is 280 mg/m^2 and for ≥ 80 years, 250 mg/m^2. The proposed product information was also updated.

If it is decided to register the product, registration will be conditional on implementation of the final RMP agreed with the TGA Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

Vinflunine is extensively distributed to tissues, has low and variable metabolism and is cleared slowly through both the liver and kidney. Mean terminal half-life is 40 h for vinflunine and 120 h for the active metabolite DVFL. Dose adjustment is recommended in both liver and renal impairment.

In the pivotal efficacy study (VFL302), vinflunine did not significantly increase overall survival, the primary endpoint. PS was 0 or 1. In an analysis which adjusted for prognostic factors and an analysis in an “eligible patient population” which excluded major protocol violators, there was a marginally statistically significant increase in overall survival (median 2 months). There were significant but modest increases in tumour response rate and progression-free survival. Similar overall survival was achieved in two uncontrolled supportive studies (VFL202, CA001).

Safety information from the three trials was pooled for an overall population of 450 patients. Vinflunine caused a high incidence of severe haematological and gastrointestinal effects. Serious cardiac reactions and peripheral neuropathy were common. Six deaths (1%) were related to vinflunine.

Given the small benefit and considerable toxicity of vinflunine, the benefit-risk balance is

unfavourable.

Delegate's Draft Decision

The Delegate recommended rejection of the application to register vinflunine ditartrate (Javlor) injection for second line treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen on the grounds that efficacy and safety have not been satisfactorily established.

The application was submitted to ACPM for advice.

Response from Sponsor

The sponsor provided the following response:

1. Benefit-Risk Balance:

The pivotal phase III study (VFL 302) of VFL + BSC vs BSC is the first phase III study ever performed in the advanced TCCU after failure of a prior platinum-containing regimen.
In this phase III study, VFL in monotherapy has been demonstrated to give a statistically significant prolongation of survival of 2.6 months compared to BSC (4.9 months vs 4.3 months) in the eligible patients which represent the targeted population by the protocol. The survival analysis in this population is methodologically acceptable as being a comparison of randomised groups as the violations cannot be as result of treatment. This survival benefit was also seen in the pre-specified multivariate analysis performed in the ITT population and the pre-specified patient subgroups. Finally, reduced incidence of pain with reduced need for radiotherapy was observed.
When compared to recently approved drugs in comparable diseases with short life expectancy, the therapeutic effect (OS and PFS) reported with VFL are of clinical meaningful relevance.
The overall safety of VFL single agent is based on 1203 patients (4617 cycles) and 450 advanced TCCU patients refractory or relapsing after a prior platinum-containing regimen. The most frequently observed adverse events are neutropenia, anaemia, constipation and asthenia/fatigue.
Neutropenia is the only dose limiting toxicity but was rarely associated with complications as febrile neutropenia and/or infection. Neutropenia and aneamia are familiar AEs for physicians in the field of oncology and may be managed by a variety of medical measures such as G-CSF, and blood transfusions. In all cases a close monitoring of haematological parameters is required during treatment.
Even being the most common gastrointestinal adverse events, constipation is non cumulative, reversible and manageable with prophylactive measures, laxatives used in a curative manner and dose adjustment. In any case, it was shown that constipation is associated with a relative absence of major clinical consequences.
Other safety signals observed were arrhythmia and cardiac infarction which rarely occurred and above all in patients with metabolic, cardiovascular and pulmonary histories. Special caution will be exercised as for the other vinca alkaloids when patients with prior cardiac ischaemic disease or angina pectoris will be treated with VFL.
In summary given the acceptable and manageable safety profile of VFL, the meaningful efficacy benefits establish a positive benefit-risk ratio for VFL in the claimed indication.

2. With respect to an explanation for the deletions of adverse reactions not in a group the sponsor provided the following answer:

It was a recommendation by the RMP evaluator that information on ARs was consistent with those listed in the most recent EU SPC. Table 2 in the Australian PI is exactly comparable with the same table in the current European SPC. The inclusion of ARs in section « Undesirable effects » of Javlor EU SPC is based on the "Guideline on SPC" (October 2005 and September 2009) which mentions that *"Adverse events, without at least a suspected causal relationship, should not be listed in the SPC* (p.15/29*)"*
All ARs reported during vinflunine clinical trials and presented in this application, have been coded with MedDRA dictionary at the nearest of the investigators' reported terms. Sometimes reported terms were too undefined and concerned adverse events which may have been induced by various causes. It was not possible to connect accurately these events to vinflunine, but as causal relationship could not be ruled out with certainty, they were attributed to vinflunine in conservative manner. This situation was observed during clinical trials in TCCU indication as well as in other indications. Of note, these ARs, which are not listed in the PI and are not part of the ARs grouping, have been reported most of the time once or twice. Based on those arguments and in order to provide health care professionals with the most accurate and useful information, ARs for which the causal relationship with vinflunine was not considered as at least a reasonable possibility have not been reported in the section "Adverse Effects" of the Javlor PI.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Pierre Fabre Medicament Australia Pty Ltd to register the new chemical entity vinflunine ditartrate (JAVLOR) concentrated injection 50 mg/2 mL, 100 mg/4 mL and 250 mg/10 mL for the indication:

Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

The ACPM noted that evidence of survival benefit was significant but that toxicity was high, however, that this would be the only treatment available for this indication. Post-market collection of efficacy and safety data is important.
The ACPM advised that the issue of dose was important as patients could deteriorate quickly and toxicity would then become a major factor with this product.
Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

- Amendments to the Dosage and Administration section to clearly state the need to initiate treatment on a lower dose for certain patient groups but permitting escalation if excessive toxicity is not experienced, to a maximum of 320 mg/m2.
- Amendments to the Precautions and Contraindications sections clearly stating that treatment should be stopped if patient develops ≥ Grade 3 neuropathy.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Javlor containing vinflunine ditartrate 50mg/2mL, 100mg/4mL, and 250mg/10mL concentrated injection, indicated for:

Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

Attachment 1. Product Information

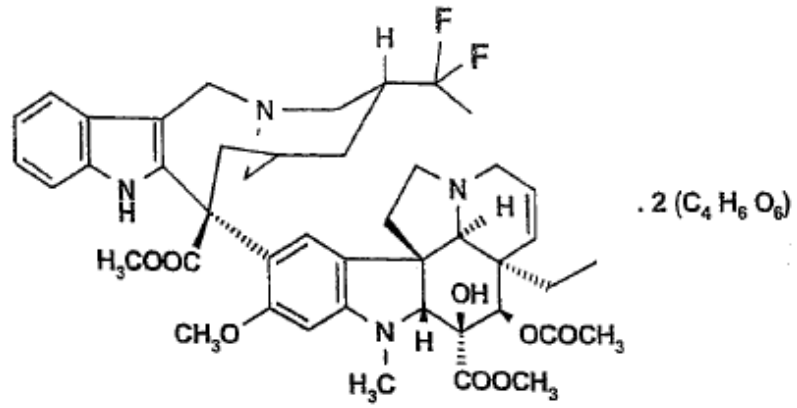
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

JAVLOR®
25 mg/mL Concentrated Injection

NAME OF THE MEDICINE

vinflunine ditartrate



CAS number: 194468-36-5

DESCRIPTION

Vinflunine ditartrate is a white to off-white powder with the molecular formula $C_{53}H_{66}F_2N_4O_{20}$ and a molecular weight of 1117.09. Vinflunine ditartrate is freely soluble in water, soluble in ethanol and practically insoluble in dichloromethane. It is very hygroscopic with a pKa value of 5.67 and 8.17 in water at 26°C – 27°C.

Javlor® Concentrated Injection is presented as a clear, colourless to pale yellow solution. It is supplied as a sterile, endotoxin-free aqueous solution intended for dilution with a suitable parenteral fluid (sodium chloride 0.9% solution or glucose 5% solution). One mL of Javlor® contains 25 mg of vinflunine (as vinflunine ditartrate). Javlor® also contains the excipient, water for injections.

PHARMACOLOGY

Pharmacodynamics

Vinflunine is an antineoplastic drug. 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 dynamics, mitotic arrest and apoptotic cell death.

In vivo, vinflunine displays significant antitumour activity against a broad spectrum of human xenografts in mice both in terms of survival prolongation and tumour growth inhibition.

Pharmacokinetics

Vinflunine pharmacokinetics is linear up to 400 mg/m^2 in cancer patients. Blood exposure to vinflunine (AUC) significantly correlated with severity of leucopenia, neutropenia and fatigue.

Distribution

Vinflunine is moderately bound to human plasma protein (67.2 ± 1.1%) with a plasma/blood concentration ratio of 0.80 ± 0.12. Protein binding mainly involves high density lipoproteins and serum albumin and is non-saturable in 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: 35 ± 9 L/kg suggesting extensive distribution into tissues.

Metabolism

All metabolites identified are formed by the cytochrome CYP3A4 isoenzyme except for 4-O-deacetylvinflunine (DVFL) which is formed through multiple esterases. DVFL is the only major active metabolite in blood.

Elimination

Vinflunine is eliminated following a multi-exponential concentration decay with a terminal half-life ($t_{1/2}$) close to 40 h. DVFL is slowly formed and more slowly eliminated than vinflunine ($t_{1/2}$ of 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 (coefficients of variation of 25% and 8% respectively).

CLINICAL TRIALS

The efficacy of vinflunine as second line therapy for the treatment of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen and with a Performance Status of ≤ 1

was demonstrated in one phase III (VFL 302) and two phase II (VFL 202 and CA 001) clinical trials.
The phase III clinical trial was an open-label, randomised, multi-centre study comparing vinflunine plus best supportive care to best supportive care (BSC) alone in patients with advanced TCCU previously treated with a first-line platinum-containing chemotherapy. Two hundred and fifty three patients were randomised to the vinflunine + BSC arm and 117 patients to the BSC arm. The vinflunine dose was 320 mg/m^2 for patients with performance status of 0 and without previous pelvic irradiation and 280 mg/m^2 escalated to 320 mg/m^2 for patients with performance status of 1 or previous pelvic irradiation. The dose was given by intravenous infusion over 20 minutes every 3 weeks.

Vinflunine did not significantly increase overall survival, the primary endpoint, in the intent-to-treat analysis. There was a small significant increase in progression-free survival of median 1.5 months (Table 1).

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 (performance status (PS), visceral involvement, alkaline phosphatases, haemoglobin, pelvic irradiation) were taken into consideration (Table 1). A statistically significant difference in overall survival with vinflunine treatment (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) (Table 1).

Table 1. Efficacy Results of the Phase III Trial (VFL 302) – Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract 2nd Line.

	VFL + BSC	**BSC**	**Difference/Hazard Ratio [95% CI]**
Evaluable Patients	n = 185	n = 85	
Overall Response Rate[1] (Complete + Partial) %	8.6 (0 + 8.6)	0 (0+0)	8.6 [5.0, 13.7]
Intent-to-Treat	n = 253	n = 117	
Progression-Free Survival[1] *median months*	3.0	1.5	p = 0.0012
Overall Survival *median months*	6.9	4.6	0.88 [0.69, 1.12]
Overall Survival (adjusted)[2]			0.77 [0.61, 0.98]

Eligible Patients	n = 249	n = 108	
Overall Survival *median months*	6.9	4.3	0.78 [0.61, 0.99]

VFL: Vinflunine; BSC: Best Supportive Care; [1] Independent Review; [2] Cox proportional hazards model.

In the two multi-centre, open-label, single-arm phase II clinical trials, a total of 202 patients were treated with vinflunine (VFL 202: n=51, CA 001: n=151). The median progression-free survival was 3.0 months and 2.7 months respectively. The median survival was 6.6 months and 7.9 months respectively.

INDICATIONS

Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

CONTRAINDICATIONS

- Hypersensitivity to vinflunine or other vinca alkaloids.
- Recent (within 2 weeks) or current severe infection.
- Baseline absolute neutrophil count (ANC) < 1.5 x 10^9/L or platelets < 100 x 10^9/L
- Lactation (see PRECAUTIONS – Use in lactation).

PRECAUTIONS

Performance Status

Vinflunine has a narrow safety threshold. If vinflunine is used in patients with poor performance status or patients likely to progress quickly to poor performance status, close observation is required since toxicity may be excessive.

For patients with WHO/ECOG performance status 1, vinflunine dose reduction is recommended (see DOSAGE AND ADMINISTRATION).

For patients with WHO/ECOG performance status 2 or greater, physicians should carefully consider the benefits and risks of vinflunine since there is no experience of the use of vinflunine in such patients.

Haematological toxicity

Neutropenia, leukopenia, anaemia and thrombocytopenia are frequent adverse reactions of vinflunine. Complete blood counts should be checked before each vinflunine infusion.

The recommended dose should be reduced in patients with Grade > 3 haematological toxicity (see DOSAGE AND ADMINISTRATION).

Javlor should not be administered when the ANC is < 1 x 10^9/L or and/or platelets < 100 x 10^9/L.

Gastrointestinal disorders
Severe constipation (grade ≥ 3) occurred in 15.3% of treated patients. Constipation is reversible and can be prevented by special dietary measures such as oral hydration, fibre intake and the administration of laxatives such as stimulant laxatives or faecal softners from day 1 to day 5 or 7 of the treatment cycle.

For patients at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior abdominal surgery), an osmotic laxative should be administered once a day from day 1 to day 7 in the morning before breakfast.

In the case of Grade 2 mucositis or constipation for ≥ 5 days or any Grade ≥ 3 gastrointestinal toxicity (except nausea or vomiting), the dose of vinflunine should be reduced (see DOSAGE AND ADMINISTRATION).

Neuropathy
Neuropathy is a frequent adverse effect of vinflunine. Patients should be monitored for symptoms and signs of neuropathy before each vinflunine infusion. In the case of Grade 2 neuropathy (weakness or sensory disturbance not interfering with activities of daily living), the vinflunine dose should be reduced (see DOSAGE AND ADMINISTRATION).In the case of Grade ≥ 3 neuropathy (weakness or sensory disturbance interfering with activities of daily living), vinflunine treatment should be discontinued.

Cardiac disorders
Few QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhythmias although no ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increased proarrhythmic risk (e.g. congestive failure, known history of QT interval prolongation, hypokalemia) ((see ADVERSE EFFECTS). The concomitant use of two or more QT/QTc interval prolonging substances is not recommended (see PRECAUTIONS – Interactions with other medicines).

Special attention is recommended when vinflunine is administered to patients with a prior history of myocardial infarction/ischemia or angina pectoris (see ADVERSE EFFECTS). Ischaemic cardiac events may occur, especially in patients who have underlying cardiac disease. Thus patients receiving vinflunine 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.

Venous irritation

When infused through a peripheral vein, vinflunine can induce Grade 1 (22.0% of patients, 14.1% of cycles), Grade 2 (11.0% of patients, 6.8% of cycles) or Grade 3 (0.8% of patients, 0.2% of cycles) venous irritation. All cases resolved rapidly without treatment discontinuation. Instructions for administration should be followed as described in "DOSAGE AND ADMINISTRATION – Administration of vinflunine".

Special populations

Hepatic impairment

No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients with mild to moderate hepatic impairment compared to patients with normal hepatic function. This was further confirmed by a population pharmacokinetic analysis which demonstrated an absence of relationship between vinflunine clearance and biology markers of hepatic impairment. However, lower vinflunine doses are recommended in patients with mild to moderate hepatic impairment because the standard vinflunine dose was not tolerated (see DOSAGE AND ADMINISTRATION). Vinflunine is not recommended in severe hepatic impairment.

Renal impairment

A pharmacokinetic phase I study in patients with renal impairment is ongoing. An interim analysis on 13 patients with moderate impairment (40 mL/min ≤ creatinine clearance ≤ 60 mL/min) and on 9 patients with severe impairment (20 mL/min ≤ creatinine clearance < 40 mL/min) indicated a decreased elimination of both vinflunine and DVFL when creatinine clearance is decreased. This was further confirmed by a population pharmacokinetic analysis which included 56 patients with a creatinine clearance between 20 mL/min and 60 mL/min which showed that vinflunine clearance is influenced by the creatinine clearance value (Cockcroft and Gault formula). Therefore the recommended dose should be reduced in patients with moderate and severe renal impairment (see DOSAGE AND ADMINISTRATION).

Elderly (≥ 75 years)

A pharmacokinetic phase I study of vinflunine was performed in elderly patients (n=46). Vinflunine doses were adjusted according to 3 age groups as shown below:

Age (y)	Number of patients	Vinflunine (mg/m²)
[70 – 75]	17	320
[75 – 80]	15	280
≥ 80	14	250

Vinflunine clearance was significantly decreased in patients ≥ 80 years old as compared to a control group of younger patients < 70 years. Pharmacokinetics of VFL were not modified for patients ≥ 70 and < 75 years old and patients ≥ 75 and < 80 years old.

Based on both PK and safety data, dose reductions are recommended in the elder groups: ≥ 75 and < 80 years old; and ≥ 80 years old. For further cycles, the dose should be adjusted in the event of toxicity (see DOSAGE AND ADMINISTRATION).

Paediatric use
The safety and effectiveness of vinflunine has not been established in patients below the age of 18 years. The subject indication does not apply to children.

Other
According to the population pharmacokinetic analysis, neither gender nor patient performance status (ECOG score) had an impact on vinflunine clearance which is directly proportional to body surface area.

Effects on fertility
There are no human data on the effects of vinflunine on male or female fertility. In animal studies, adverse effects on the male reproductive system of rats were observed at clinically-relevant systemic exposures. Both male and female patients with reproductive potential should take adequate contraceptive measures during treatment and for three months after the discontinuation of therapy. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine.

Use in pregnancy
Category D

There are no data available on the use of vinflunine in pregnant women. Studies in rats and rabbits have shown embryotoxicity and teratogenicity at subclinical exposures. On the basis of the results of animal studies and the pharmacological action of vinflunine, 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.

Use in lactation
It is not known whether vinflunine or its metabolites are excreted in breast milk. In animal studies, adverse effects on postnatal development were seen in rat pups. Therefore, because of the potential harm to infants, breast feeding during treatment with vinflunine is contraindicated.

Carcinogenicity
The carcinogenic potential of vinflunine has not been studied. However, positive findings in genotoxicity assays suggest that vinflunine may have a carcinogenic potential.

Genotoxicity
Vinflunine was shown to be clastogenic (induces chromosome breakage) in a rat micronucleus test as well as mutagenic and clastogenic in mouse lymphoma assay. Negative results were obtained in bacterial mutagenicity assays (Ames test).

Interactions with other medicines
In vitro studies showed that vinflunine neither induced CYP1A2, CYP2B6 or CYP3A4 activity nor inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity.

In vitro studies showed that vinflunine is a Pgp-substrate like the other vinca alkaloids. The clinical relevance of this is unknown.

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

A phase I study evaluating the effect of ketoconazole treatment (a strong CYP3A4 inhibitor) on vinflunine pharmacokinetics indicated that co-administration of ketoconazole (400 mg p.o. once daily for 8 days) induced a 30% and 50% increase of both vinflunine and DVFL blood exposures respectively.

Therefore the concomitant use of vinflunine and potent CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole and grapefruit juice) or inducers (such as rifampicin and Hypericum perforatum (St John's wort)) should be avoided as they may increase or decrease vinflunine and DVFL concentrations.

The concomitant use of vinflunine with other QT/QTc interval prolonging drugs or pro-arrhythmic drugs should be avoided (see PRECAUTIONS – Cardiac disorders).

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 to the liposomes and a modified blood distribution of both compounds. Therefore, caution should be exercised when this type of combination is used.

A possible interaction with paclitaxel and docetaxel (CYP3A 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 conducted.

The concomitant use of opioids could enhance the risk of constipation.

Effects on ability to drive and operate machinery

The effect of vinflunine on the ability to drive and use machines has not been studied. However, patients should be advised not to drive or operate machinery if they experience any adverse reactions with a potential impact on their ability to perform these activities (e.g. dizziness and syncope are common).

ADVERSE EFFECTS

The most frequent treatment-related adverse reactions reported in the one phase III and two phase II trials in patients with transitional cell carcinoma of the urothelium (450 patients treated with vinflunine) were haematological disorders, mainly neutropenia, anaemia; gastrointestinal disorders, especially constipation, anorexia, nausea, stomatitis/mucositis, vomiting, abdominal pain and diarrhoea; and general disorders such as asthenia/fatigue.

Adverse reactions are listed in Table 2 by System Organ Class, frequency and grade of severity (NCI CTC (National Cancer Institute Common Terminology Criteria) version 2.0).

Frequency of adverse reactions is defined as: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions observed in patients with transitional cell carcinoma of the urothelium treated with vinflunine.

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
Infections and infestations	Common	neutropenic infection	3.8	3.8
		infections (viral, bacterial, fungal)	6.9	2.7
	Uncommon	neutropenic sepsis	0.2	0.2
Blood and lymphatic system disorders	Very common	neutropenia	79.6	54.6
		leucopenia	84.5	45.2
		anaemia	92.8	17.3
		thrombocytopenia	53.5	4.9
	Common	febrile neutropenia	6.7	6.7
Immune system disorders	Common	hypersensitivity	1.8	0.2
Metabolism and nutrition disorders	Very common	anorexia	34.4	2.7
	Common	dehydration	4.4	2.0
Psychiatric disorders	Common	insomnia	5.1	0.2
Nervous system disorders	Very common	peripheral sensory neuropathy	9.8	0.9
	Common	syncope	1.1	1.1
		headache	6.2	0.7
		dizziness	5.3	0.4
		neuralgia	6.0	0.4
		dysgeusia	3.1	0
		neuropathy	1.8	0
	Uncommon	peripheral motor neuropathy	0.7	0
Eye disorders	Uncommon	visual disturbance	0.4	0
Ear and labyrinth disorders	Common	ear pain	1.3	0
	Uncommon	vertigo	0.9	0.4
		tinnitus	0.9	0
Cardiac	Common	tachycardia	1.8	0.2

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
Disorders	Uncommon	myocardial ischaemia	0.7	0.7
		myocardial infarction	0.2	0.2
Vascular Disorders	Common	hypertension	3.3	1.8
		vein thrombosis	3.3	0.4
		hypotension	1.1	0.2
Respiratory, thoracic and mediastinal disorders	Common	dyspnoea	4.2	0.4
		cough	2.2	0
	Uncommon	acute respiratory distress syndrome	0.2	0.2
		pharyngolaryngeal pain	0.9	0
Gastro-intestinal Disorders	Very common	constipation	54.9	15.3
		abdominal pain	21.6	4.7
		vomiting	27.3	2.9
		nausea	40.9	2.9
		stomatitis	26.9	2.7
		diarrhoea	12.9	0.9
	Common	ileus	2.7	2.2
		dysphagia	2.0	0.4
		buccal disorders	4.7	0.2
		dyspepsia	5.6	0.2
	Uncommon	odynophagia	0.4	0.2
		gastric disorders	0.9	0
		oesophagitis	0.4	0.2
		gingival disorders	0.7	0
Skin and Subcutaneous Tissue Disorders	Very common	alopecia	28.7	NA
	Common	cutaneous reaction	3.1	0
		pruritus	1.3	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		hyperhidrosis	1.1	0
	Uncommon	dry skin	0.9	0
Musculoskeletal and Connective Tissue Disorders	Very common	myalgia	16.4	3.1
	Common	muscular weakness	2.2	0.9
		arthralgia	8.0	0.7
		back pain	4.9	0.4
		jaw pain	3.3	0.0
		pain in extremities	3.3	0
		bone pain	2.4	0
		musculoskeletal pain	2.0	0
Renal and Urinary Disorders	Uncommon	renal failure	0.2	0.2
General Disorders and Administration Site Conditions	Very common	asthenia/fatigue	55.3	15.8
		injection site reaction	27.6	0.4
		pyrexia	10.9	0.4
	Common	chest pain	4.4	0.9
		chills	2.2	0.2
		pain	3.6	0.2
		oedema	1.3	0
	Uncommon	extravasation	0.7	0
Investigations	Very common	weight loss	24.0	0.4
	Uncommon	transaminases increased	0.4	0
		Weight gain	0.2	0

Adverse reactions in other indications

In other indications (n=753), the adverse reaction profile of vinflunine was similar to that in transitional cell carcinoma of the urothelium except for the following additional reaction:

Endocrine disorders
Uncommon: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH).

DOSAGE AND ADMINISTRATION

Javlor Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Before each cycle, adequate monitoring of complete blood counts should be conducted to verify the absolute neutrophil count (ANC) value as neutropenia is a frequent adverse reaction of vinflunine.

Recommended dose

The recommended dose is 320 mg/m^2 as a 20 minute intravenous infusion every 3 weeks.

For patients with WHO/ECOG performance status (PS) of 1 or prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m^2. In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose can be increased to 320 mg/m^2 every 3 weeks for subsequent cycles.

Dose adjustment due to toxicity

Table 3: Dose adjustment due to toxicity

Toxicity	**Dose adjustment**				
(NCI CTC v 2.0)*	**Javlor initial dose of 320 mg/m^2**			**Javlor initial dose of 280 mg/m^2**	
	First event	2nd consecutive event	3rd consecutive event	First event	2nd consecutive event
Neutropenia Grade 4 (ANC < 500/mm^3) > 7 days.					
Febrile neutropenia (ANC < 1,000/mm^3) and					

fever ≥ 38.5°C)	280 mg/m^2	250 mg/m^2	Treatment discontinuation	250 mg/m^2	Treatment discontinuation
Neuropathy Grade 2					
Mucositis or constipation Grade 2 ≥ 5 days or Grade ≥ 3 of any duration.					
Any other toxicity Grade ≥ 3 (except Grade 3 vomiting or nausea).					

***NCI CTC = National Cancer Institute Common Toxicity Criteria**

In the case of Grade ≥ 3 neuropathy, vinflunine treatment should be discontinued.

In patients with ANC < 1 x 10^9/L or platelets < 100 x 10^9/L on the day of administration, the treatment should be delayed until recovery (ANC ≥ 1 x 10^9/L and platelets ≥ 100 x 10^9/L). If recovery has not occurred within 2 weeks, the treatment should be discontinued.

In the case of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) for more than 7 days or febrile neutropenia, dose adjustment is recommended (see Table 3).

In the case of Grade ≥ 2 organ toxicity on the day of infusion, treatment should be delayed until recovery to Grade 0, 1 or initial baseline status.

Dose adjustment in special populations.

Hepatic impairment

Vinflunine pharmacokinetics are not modified in patients with mild to moderate hepatic impairment (see PRECAUTIONS, Special Populations**).** However, based on hepatic parameter modifications following vinflunine administration (gamma glutamyl transferases (GGT), transaminases, bilirubin), the dose recommendations are as follows:

Table 4: Dose adjustment for hepatic impairment

Level and dose	Child Pugh Grade		Prothrombin time		Bilirubin		Transaminases		GGT
Very Mild 320 mg/m^2	-	-	> 70% NV	and	> ULN and ≤ 1.5 x	and/or	> 1.5 x ULN and ≤ 2.5 x ULN	and/or	> ULN and ≤ 5 x ULN

					ULN				
Mild 250 mg/m^2	A	or	≥ 60% NV	and	> 1.5 x ULN and ≤ 3 x ULN	and	> ULN	and/or	> 5 x ULN
Moderate 200 mg/m^2	B	or	≥ 50% NV	and	> 3 x ULN	and	> ULN	and	> ULN

NV = Normal value ULN = Upper limit of normal

Vinflunine has not been evaluated in patients with severe liver dysfunction such as patients with Child-Pugh Grade C, or patients with prothrombin time < 50% NV or with bilirubin > 5 x ULN or with transaminases > 6 x ULN or with gamma glutamyl transferases (GGT) > 15 x ULN.

Renal impairment

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

For patients with moderate renal impairment (40 mL/min ≤ creatinine clearance ≤ 60 mL/min), the recommended dose is 280 mg/m^2 given once every 3 weeks.

For patients with severe renal impairment (20 mL/min ≤ creatinine clearance < 40 mL/min), the recommended dose is 250 mg/m^2 given once every 3 weeks.

Elderly (≥ 75 years)

No age-related dose modification is required in patients less than 75 years old (See PRECAUTIONS, Special Populations).

In patients at least 75 years old but less than 80 years, the recommended dose is 280 mg/m² every 3 weeks.

In patients 80 years or older, the recommended dose is 250 mg/m² every 3 weeks.

For further cycles, the dose should be adjusted in the event of toxicity, as shown in Table 5 below:

Table 5: Dose adjustment due to toxicity in elderly patients

Toxicity	**Dose adjustment**	
(NCI CTC v 2.0)*	**Vinflunine initial dose of**	**Vinflunine initial dose of**

	280 mg/m²		250 mg/m²	
	First Event	2nd consecutive event	First Event	2nd consecutive event
Neutropenia Grade 4 (ANC < 0.5 x 10^9/L) > 7 days	250 mg/m²	Definitive treatment discontinuation	225 mg/m²	Definitive treatment discontinuation
Febrile neutropenia (ANC < 1 x 10^9/L 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)				

***NCI CTC = National Cancer Institute Common Toxicity Criteria**

Administration

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

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

Recommended co-medication

In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 following each Javlor administration (see PRECAUTIONS – Gastrointestinal disorders).

General precautions for preparation and administration

As with other cytotoxic compounds, caution should be excercised when handling Javlor. Procedures for proper handling and disposal of anticancer medicines should be used. Several guidelines on this subject have been published.

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood. The use of gloves, goggles and protective clothing is recommended. If the Javlor solution comes in contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If it comes into contact with mucous membranes, the membranes should be flushed thoroughly with water.

Javlor should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Javlor.

Dilution of the Javlor concentrate

The volume of Javlor concentrate corresponding to the calculated dose of Javlor should be mixed in a 100 mL bag of 0.9% Sodium Chloride Injection, USP (saline solution) or 5% Glucose Injection, USP (glucose solution).

To reduce microbiological hazard, Javlor should be used immediately after dilution. If storage is necessary, store at $2^{o}C$ – $8^{o}C$ for not more than 24 hours.

Administration of Javlor

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

The diluted solution of Javlor should be administered as follows:

- Venous access should be established for a 500 mL bag of saline/glucose solution in the upper part of the forearm or via the central venous arm line. The veins of the hand and those close to joints should be avoided.
- The intravenous infusion should be started with 100 mL of the 500 mL bag of saline/glucose solution at a free flowing rate to assess the patency of the vein;
- The Javlor solution should be piggy-backed to the side injection port closest to the 500 mL bag to further dilute Javlor during administration;
- The Javlor solution should be infused over 20 minutes;
- The flow rate of the saline/glucose solution during the Javlor infusion should be minimal (between 60 mL/h and 120 mL/h);
- The patency of the vein should be assessed frequently and extravasation precautions should be maintained throughout the infusion;
- After the Javlor infusion is completed, in order to adequately flush the vein, the remaining solution from the saline/glucose infusion bag (250 mL minimum) should be run at a flow rate of 300 mL/h.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

OVERDOSAGE

The main toxic effect of an overdose of vinflunine is bone marrow suppression with a risk of severe infection.

There is no known antidote for overdoses of vinflunine. In the case of an 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.

PRESENTATION

Javlor Concentrated Injection is a clear, colourless to pale yellow solution containing 25 mg vinflunine per mL. Javlor Concentrated Injection is available in 50 mg/2 mL, 100 mg/4 mL* and 250 mg/10 mL single use vials. It is packaged in clear glass vials (type 1), closed with a rubber stopper and sealed with an aluminium seal. Javlor Concentrated Injection is supplied in packs of 1 and 10 vials.

STORAGE CONDITIONS

Store at 2^{o}C to 8^{o}C (Refrigerate. Do not freeze)
Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

S4

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11 February 2011

* Not marketed

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