Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Phase II study assessing the maintenance treatment with vinflunine after first-line therapy with gemcitabine and cisplatin in patients with advanced or metastatic transitional cell carcinoma of the urothelial tract

Investigational product: L00070 / vinflunine ditartrate / IV

Study Design: Prospective, open-label, multicentre, single arm trial

EudraCT number: **2011-000272-34**

Protocol number: L00070 IN 214 P1

Phase of development: Phase II

Date of first enrolment: February 17th, 2012

Date of last completed: February 28th, 2014

Co-ordinator(s):
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Date of report: 17/12/2017

Study performed in compliance with Good Clinical Practice.

Final Version - 17.12.17

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Javlor® Concentrate for Solution for Infusion	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: Vinflunine	**Vol.: .....Page: .....**	

Title of study:	Phase II study assessing the maintenance treatment with vinflunine after first-line therapy with gemcitabine and cisplatin in patients with advanced or metastatic transitional cell carcinoma of the urothelial tract. **[short title: JASiMA - JAVLOR® Switch in Maintenance]**	
Principal Investigators:	Maike DE WIT, MD Mark SCHRADER, MD	
Study centre(s):	22 centres/11 active centres (8 in Germany, 2 in Austria and 1 in Italy) List of sites and investigators is provided in Appendix 16.1.4	
Publication (reference):	None	
Studied period:	First enrollment: February17th , 2012 Last enrollment: July 24th, 2013 Last completed: January 28th, 2014 Cut off date for analysis: May 13th, 2015	**Phase of development:** phase II, single arm, open-label
Objectives: **Primary:** **Secondary:**	Primary objective: Progression-Free survival rate (PFS-R) at 3 months after registration. Secondary objectives: - Overall response rate (ORR), duration of response, duration of stable disease - Response upgrade rate, disease control rate (DCR), duration of disease control - Progression-free survival time (PFS), Time to treatment failure (TTF) - Overall survival tome (OS) - Quality of life (QoL) using EORTC QLQ-C30 questionnaire - Safety and tolerability	
Methodology:	**Phase II, single-arm, open-label, European trial** The 1st line GC-therapy is not part of the trial. Inclusion into the trial took place only after completion of 4 cycles of GC treatment for patients showing SD, PR or CR under this 1st line treatment.	
Number of patients (planned and analysed):	Planned= 70 evaluable patients Included = 20 patients (due to lack of recruitment, the study was stopped before the 1st step Fleming design.	

	N (%)
Registered patients	20 (100)
Treated patients*	19 (95.0)
Eligible patients**	19 (95.0)
Intent to Treat population (ITT)	19 (95.0)
Evaluable patients for tumor response	15 (75.0)
Evaluable patients for safety analysis	19 (95.0)
Evaluable patients for QoL analysis	15 (75.0)

*One screen failure, ** one patient not eligible (Pt≠060602): registration done after the first study drug administration

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Diagnosis and main criteria for inclusion:	**(to be eligible, all of the below criteria must be fulfilled):** 1) Patients aged ≥ 18 years. 2) Histologically confirmed diagnosis of locally advanced or metastatic predominantly transitional cell carcinoma of the urothelium (TCCU) [urinary bladder, kidney, renal pelvis, or ureter]. Not amenable to definitive local/regional therapy. 3) Stable Disease, Partial Response or Complete Response as outcome of 1st line treatment with the gemcitabine-cisplatin combination for advanced/metastatic TCCU (confirmed or not). 4) Completion of 4 cycles of 1st line treatment with the gemcitabine-cisplatin combination for the chemo-naïve advanced/metastatic TCCU patient and no persistence of any adverse event > Grade 1 related to this treatment. 5) Last administration of gemcitabine and cisplatin (i.e. last day of administration of both compounds) ≤ 6 weeks **before registration.** 6) The patient must give written (personally signed and dated) informed consent before completing any study-related procedure which means any assessment or evaluation that would not be part of the routine medical care of the patient. 7) Women of childbearing potential must be using a medically accepted method of contraception (i.e. hormonal contraceptives, intrauterine devices) to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and for up to 3 months after the last dose of study treatment in such a manner that the risk of pregnancy is minimised. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the start of study treatment. 8) Fertile men must be using an effective method of birth control, if their partners are women of childbearing potential, during the study period and up to 3 months after last administration of study medication. 9) ECOG performance status of **0 or 1** (patients aged ≥ 80 years with ECOG performance status 1 or ECOG performance status 0 and prior irradiation of the pelvic area are not eligible) 10) Estimated life expectancy of **at least 3 months** 11) Adequate haematological, renal and hepatic functions as evidenced by: - Absolute Neutrophil Count ≥ 1,500/mm^3 (≥ 1.5 x 10^9/L) - Haemoglobin ≥ 9g/dL - Platelet count ≥ 100,000/mm^3 - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) - Transaminases ≤ 2.5 x ULN* [≤ 5 times ULN only in case of liver metastasis] - Alkaline phosphatase ≤ 5 x ULN - Calculated creatinine clearance (CrCL) (Cockroft-Gault) : • ≥ 20 mL/min for age < 75 years • ≥ 40 mL/min for age ≥ 75 to < 80 years • > 60 mL/min for age ≥ 80 years

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Exclusion criteria	1) Patients aged < 18 years. 2) Patients with predominantly non-TCCU (adenocarcinoma, squamous cell carcinoma or other). 3) Prior administration of any systemic anti-tumour therapy (other than Gemcitabine-cisplatin combination) for treatment of TCCU. 4) Progressive Disease during or after 1st line treatment with the gemcitabine-cisplatin combination for advanced/metastatic TCCU. 5) Known brain metastasis or leptomeningeal involvement (CT Scan/MRI not required to rule this out unless there is clinical suspicion of CNS disease). 6) Peripheral neuropathy ≥ Grade 2. 7) Any serious, concurrent illness or uncontrolled medical disorder including active infection requiring antibiotics **within 2 weeks before registration**, uncontrolled cardiac arrhythmia, unstable diabetes mellitus, uncontrolled hypercalcaemia, congestive heart failure, poorly controlled hypertension, unstable angina pectoris, or myocardial infarction **within 6 months before registration**. 8) Screening-electrocardiogram with any significant modifications suggesting a high risk of occurrence of an acute clinical event (such as angina pectoris, high risk arrhythmia, etc.). 9) Prior other malignancy. Note: Patients who have had another malignancy and who have been disease-free for at least 3 years or patients with a history of successfully treated basal cell carcinoma of the skin or in-situ cervix carcinoma or localised prostate cancer with limited risk of recurrence (pT ≤ 2b, Gleason score ≤ 7) that was incidentally discovered and did not lead to any other treatment apart from prostatectomy are eligible. 10) Known hypersensitivity to vinca alkaloids. 11) Prior radiation to ≥ 30% of the bone marrow or radiation not completed at least 28 days before registration or current persistence of any adverse event >Grade 1 related to this treatment. 12) Major surgery or trauma within 28 days before registration or presence of any major non-healing wound, fracture or ulcer. 13) Prior participation in an interventional clinical study investigating drugs within 30 days before registration and during the study. 14) Current treatment with any potent CYP3A4-inhibitor or –inducer (see Appendix 6). 15) Pregnant or lactating women or women with positive pregnancy test at screening. 16) Any serious and/or unstable pre-existing medical, psychiatric, psychological, familial, sociological, geographical or other condition that could interfere with the patient's safety, provision of informed consent, or compliance with the study protocol. 17) Prisoners or persons who are compulsory detained (involuntary incarcerated).

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Test product,
Dose,
Mode of administration,
Batch number:
	Study treatment schedule
	(a treatment cycle is defined as a period of 21 days):
	1) Patients with adequate renal function (CrCL > 60 mL/min)
	• Patients with ECOG WHO PS 0 without prior irradiation of the pelvic area:
	  • patients < 75 years : **vinflunine IV 320 mg/m²** every 21 days.
	  • patients ≥ 75 to < 80 years : **vinflunine IV 280 mg/m²** every 21 days.
	  • patients ≥ 80 years : **vinflunine IV 250 mg/m²** every 21 days.
	• Patients with ECOG WHO PS 1 and patients with ECOG WHO PS 0 with prior irradiation of the pelvic area:
	  • patients < 75 years : 1st cycle**: vinflunine IV 280 mg/m²** every 21 days. Further cycles starting from 2nd cycle: the dose could be increased to **vinflunine IV 320 mg/m²** every 21 days, only in patients who did not experience any haematological toxicity causing a treatment delay or dose reduction during the 1st cycle.
	  • patients ≥ 75 to < 80 years : **vinflunine IV 250 mg/m²** every 21 days.
	  • Patients ≥ 80 years: not eligible.
	2) Patients with moderate renal insufficiency
	(40 mL/min ≤ CrCL ≤ 60 mL/min):
	  • patients < 75 years : **vinflunine IV 280 mg/m²** every 21 days.
	  • patients ≥ 75 to < 80 years :**vinflunine IV 250 mg/m²** every 21 days.
	  • patients ≥ 80 years : not eligible.
	3) Patients with severe renal insufficiency
	(20 mL/min ≤ CrCL < 40 mL/min):
	  • patients < 80 years : vinflunine IV 250 mg/m² every 21 days
	  • patients ≥ 80 years : not eligible.
	Bach numbers: PC2012020710P003, PC2012020602P006, 2011051210P003, PC20140507 10P007, PC20110511SB0639, PC2013050602P006.

Other product, **Dose, Mode of administration,** **Batch number:**	Not applicable
Duration of treatment:	Treatment with vinflunine had to start within 6 weeks after last GC administration (i.e. within 6 weeks after day 1 of the 4th cycle of 1st line treatment). Patients had to receive at least 2 cycles of treatment and continue until progression, occurrence of unacceptable toxicity, occurrence of intercurrent illness or other reaction which would in the judgement of the investigator affect the clinical status of the patient to a significant degree and require discontinuation of the drug or until patient's wish to discontinue treatment.
Criteria for evaluation: **Efficacy:**	**Efficacy Measures** . Progression and tumour response was assessed by the investigator according to RECIST Criteria version 1.1 as follows: Assessment of lesions (measurable and non-measurable) at baseline and every 6 weeks (approximately every 2 cycles). Moreover, clinical/biological bone-related events were assessed every 6 weeks. . Duration of disease control and response were evaluated for patients showing SD/PR/CR and PR/CR, respectively.
Safety:	Physical examinations, vital signs, ECG, performance status, haematology, biochemistry, adverse events using the NCI CTC AE (version 3.0) and concomitant treatments.
Pharmacokinetic assessment:	No PK study was performed in this study

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Statistical Methods	Sample size: The one-sample multiple testing procedure for phase II clinical trials as described by Fleming was used with a null hypothesis H_0 for the true PFS-rate at 3 months of 45%, an alternative hypothesis H1 of 64%. With a type I error $\alpha \leq 5\%$ and a type II error $\beta \leq 10\%$, 70 evaluable patients were to be enrolled in this phase II study. This one-sample two-test design trial was conducted as follows: 1.The first test was to be performed after 20 evaluable patients : • if < 7 "non progressions" were observed, the H_o hypothesis was not rejected and inclusion of further patients was not needed; • if ≥ 17 "non progressions" were observed, the Ho hypothesis was rejected and further investigation of the drug in confirmatory setting was warranted; • if ≥ 7 and < 17 "non progressions" were observed, 50 more patients were needed to be evaluated. 2.The second and last test was to be performed after 70 evaluable patients : • if < 39 "non progressions" were observed, the Ho hypothesis was not rejected and further investigation of the drug was not warranted; • if ≥ 39 "non progressions" were observed, further investigation of the drug in confirmatory setting was warranted. Assuming that about 10% of patients will be non-evaluable, a total of 77 patients were to be enrolled in this phase II study. Efficacy analyses: The primary efficacy analysis was to evaluate the PFS-rate at 3 months after registration. 95% CI was provided. Analysis was performed on the intent-to-treat population (ITT) and evaluable patients. The secondary efficacy analyses were: 1. estimation of Disease Control Rate and Duration of Disease Control, 2. estimation of Objective Response Rate and Duration of Response, 3. estimation of the Response Upgrade Rate, 4. estimation of Duration of Stable Disease, 5. estimation of Progression-Free Survival, 6. estimation of Time To Treatment Failure, 7. estimation of Overall Survival

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Statistical Methods (Con't)	Safety analyses Maximum grade according to CTCAE version 3.0 or severity were tabulated, for each MedDRA "System Organ Class" (SOC) and "Preferred Term" (PT), by cycle and by patient. All analyses were performed in two different ways: regardless or not to the relationship to treatment. Quality of Life analysis QoL was evaluated through the QLQ-C30 quality of life questionnaire. Changes of the scores from baseline of the parameters were provided. Statistical methodology Descriptive methods were used to present all relevant data: • Continuous data were summarised with the following items: frequency, median, range, mean, standard deviation and standard error if relevant. • Categorical data were presented in contingency tables with frequencies and percentages of each modality (including missing data modality). 95% confidence intervals will be calculated following the exact method. Analysis of Progression-Free Survival, Duration of Response, Disease Control, Stable Disease, Time To Treatment Failure and Overall Survival were performed according to the Kaplan-Meier method. 95% confidence intervals for the median were provided

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Efficacy Results

At the cut off date for the analysis (May 13th, 2015), all patients discontinued the study. Reasons for study discontinuation were PD in 6 (30%) patients, AEs in 3 (15%) patients and other reasons mainly refusal of patient's to continue study treatment in 10 (50%) patients.

Median follow up in the study was 27.1 months [95%CI: (9.2 -27.6)]. At the cut off date for the analysis, 6 (30%) patients were still alive, 12 (60%) died (of which 1 early death) and 2 (10%) were lot to follow-up.

Patient's demographics and baseline characteristics.

Mean age of study population was 65.6 ± 8.0 years, ranging from 48.9 years and 77.4 years. Ten (52.6%) patients were aged ≥ 65 years old, between 75 and 80 years for 3 of them. There were 68.4% of male patients and the majority (57.9%) of the patients had an ECOG PS at baseline of 0.

At study entry, 16 (84.3%) patients had a metastatic disease with 1 or 2 organs involved for 13 patients (57.9%). Main organ involved was lymph nodes in 10 patients (52.6%).

All patients received prior Gemcitabine + Cisplatin (GC) chemotherapy + surgery as 1st line treatment, followed by radiotherapy to pelvic area. Best responses to 1st GC chemotherapy were: CR in one patient, PR in 13 patients and SD in 5 patients.

As regards to the medical history, more than half of the patients (57.9%) had at least 3 co-morbidities at study entry, represented mainly by blood hypertension in 26.3% of the patients, followed by pulmonary embolism in 15.8% of the patients. One patient had a history of coronary artery disease.

Most frequently reported (>10% incidence) concomitant treatments were in the alimentary tract and metabolism SOC (57.9% of the patients), followed by cardiovascular system (52.6%) and blood and blood forming organs (42.1%).

Primary efficacy endpoint: PFS-R at 3 months

PFS-R at 3 months in the ITT population and evaluable population was 82.4% [95%CI: 54.7; 93.9] and 80.0% [95% CI: 50.0%; 93.1%], respectively.

Secondary efficacy endpoints

ORR and DCR: In the ITT population, CRs were achieved in 4 patients, partial responses in 3 patients, yielding an ORR of 36.8% [95%CI: 16.3; 61.4]. In the evaluable population, the ORR was 40% [95%CI: 16.3; 67.7]. A total of 8 patients had disease stabilisation, yielding a disease control rate (DCR) of 78.9% [95%CI: 54.4; 93.9] in the ITT population and 93.3% [95%CI: 68.1; 99.8] in the evaluable population.

Upgrade rate of response: Of the 12 evaluable patients with a PR at study entry, 3 remained on PR and 3 upgraded to a CR, yielding a response upgrade rate of 33.3% One patient with a CR at study entry remained in CR during the IV vinflunine maintenance therapy. Of the 5 patients with SD at study entry, 2 remained on SD, 2 were NE, and one progressed during the vinflunine maintenance therapy.

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Efficacy Results (Con't)

Time –dependent parameters (Median [Min; Max]) in the ITT and evaluable populations:

	ITT (N=19)	Evaluable patients (N=15)
Time to first response	1.6 [1.2; 11.0]	3.0[1.4 ; 11.0]
Duration of response	16.3 [2.8 ; NR]	16.3 [2.8 ; NR]
Duration of Stable Disease	4.7 [2.5 ; 8.2]	4.7 [2.5 ; 8.2]
Duration of Disease Control	8.2 [3.9 ; 18.8]	8.2 [3.9 ; 18.8]

Survival outcomes:

In the ITT population, approximately 60% and 50% of the patients were still alive at 12 months and 18 months after the start of vinflunine maintenance therapy.

In the ITT population, with a censoring rate of 31.6% (n=6/19), median PFS was 8.3 months [95% CI/ 3.9; 17.8]. PFS rates at 6, 12 and 18 months were 58.8%, 32.7% and 26.1%, respectively. In the evaluable population, similar median PFS was reached (4 censored observation; 26.7%), with a slightly higher PFS rates at 6, 12 and 18 months as compared to the results in the ITT population.

Median OS was 19.3 months [95%CI/ 9.3; 27.3] in the ITT population (n= 8 censored observation; 42.1%) and 19.3 months [95%CI: 9.3; 27.3] in the evaluable population (n=5 censored observations, 33.3%).

Safety Results

Vinflunine delivery

Median duration of treatment with Vinflunine maintenance therapy in all treated patients (N=19) was 19.1 weeks, ranging from 3 to 86 weeks with a median of 6 cycles received by patient (range: 1 to 27 cycles). Day 1 administration of Vinflunine was delayed in only 13.2% of the cycles. Main reason for dose delay was for other reasons than toxicity (administrative reasons and patient's convenience (holidays). Dose reduction of VFL occurred in 31.6% (n=6/19) of the patients and 4.4% (n=6/155) of the cycles. All occurred in patients who had initial dose of 280 mg/m^2 (reduced to 250 mg/m^2). Main reason for dose reduction was drug related non haematological toxicity. One patient had dose escalation of Vinflunine from 250 to 280 mg/m^2.

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Safety Results (Con't)

	ITT N =19
Number of cycles	155
Median [range]	6 [1-27]
Mean (±SD)	8.2 (7.3)
Number of Pts [n, (%)]	
With at least 6 cycles	10 (52.6)
With at least 12 cycles	4 (21.1)
VFL dose administered [n, (%)]	155
by category [n, (%)]	
320 mg/m^2	48 (31.0)
280 mg/m^2	51 (32.9)
250 mg/m^2	54 (34.8)
Less than 225 mg/m^2	1 (0.6)
Missing data	1 (0.6)
VFL relative dose intensity /pt	
Median % [range]	87.1 [64.1-100.2]
Mean (SD)	86.9 (10.7)

Haematological toxicity

Haematological toxicity was common as expected. Neutropenia was reported in 14 out of the 19 treated patients (73.7 %) and in 76 out of the 143 evaluable cycles (53.2%). Anaemia occurred in 18/19 patients (94.7%) and 69.2% of the cycles, but the incidence of G3/4 anaemia was low, affecting only 2 patients (10.5%; in one cycle each). The incidence of thrombocytopenia (all grades) was low occurring in 6/19 patients (31.6%) and in 12.4% of the cycles, with no grade 3/4. One patient experienced one episode of grade 3 FN (see table below)

	NCI-CTC AE V 3.0 grading (by patient)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	1 (5.3)	12 (63.2)	4 (21.1)	2 (10.5)	0
Leucopenia	6 (31.6)	3 (15.8)	5 (26.3)	5 (26.3)	0
Neutropenia	5 (26.3)	1 (5.3)	5 (26.3)	3 (15.8)	5 (26.3)
Thrombocytopenia	13 (68.4)	5 (26.3)	1 (5.3)	0	0
Febrile Neutropenia*	-	-	-	1 (5.3)	0

*Pizzo's definition

Only two patients (10.5%) received red blood cell transfusion during study treatment.

Non Haematological toxicity

Most frequently reported related AEs (all grades) were nausea and fatigue occurring in 42.1% of the patients, each, followed by alopecia (in 36.8% of the patients) and constipation, diarrhoea and stomatitis (in 26.3% of the patients, each) and vomiting, peripheral sensory neuropathy and insomnia (in 15.8% of the patients, each).The incidence of severe (grade 3-4) drug-related AEs was low; grade 3 diarrhoea being the most common related AE by severity, occurring in 10.5% (2/19 of the patients). Grade 4 drug related toxicity consisted of stomatitis and constipation in one patient (5.3%), fatigue in one patient (5.3%), bladder pain in one patient (5.3%).

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Safety Results (Con't)	A total of 9 SAEs were reported (in 8 patients; 47.4%), of which 5 were related to study treatment. These were G3 visual acuity reduced at cycle 1 in one patient G3 arthralgia at cycle 3 in one patient, G3 fatigue at cycle 1 in one patient, and G3 constipation and G3 febrile neutropenia in one patient, both events occurred at cycle 1. One patient died during the study treatment period (within 30 days of the last study drug administration). The death was not related to study treatment but to disease progression.
Quality of Life Results	No significant differences between baseline assessments of QoL scales and assessments over study treatment for functional scales were observed. Symptoms scales showed increases in diarrhoea, appetite loss, pain and fatigue but decreases in constipation. Global health status showed no significant variation between baseline and subsequent evaluations. A trend for a slight improvement in the global health status was seen at weeks 12, 15 and 18.
General conclusion	The primary data reported in this present study are limited by the small sample size of the included patients. Nevertheless, the findings from the present study suggest that maintenance monotherapy with IV Vinflunine on day 1 every 21 days after standard platinum-based chemotherapy (GC) might be a valuable option in the treatment of patients with advanced/ metastatic TCCU. The treatment was safe and well tolerated in this small study with limited number of patients. Further investigation of vinflunine as maintenance therapy is warranted.
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