Clinical trial results:
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 (TCCU) tract.

Summary

EudraCT number	2011-000272-34
Trial protocol	DE AT IT
Global end of trial date	14 February 2015

Results information

Result version number	v1 (current)
This version publication date	16 December 2018
First version publication date	16 December 2018
Summary attachment (see zip file)	Jasima final synopsis of CSR (synopsis jasima.pdf)

Trial information

Trial identification

Sponsor protocol code	L00070-IN-214-P1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre medicament
Sponsor organisation address	45 place Abel Gance, Boulogne, France, 92100
Public contact	RIGGI, Pierre Fabre Medicament, +33 (0) 1.49.10.81.77, marcello.riggi@pierre-fabre.com
Scientific contact	RIGGI, Pierre Fabre Medicament, +33 (0) 1.49.10.81.77, marcello.riggi@pierre-fabre.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2014
Global end of trial reached?	Yes
Global end of trial date	14 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the progression-free survival-rate (PFSrate) at 3 months of IV Vinflunine (VFL) as Maintenance Therapy (MT) for patients with advanced or metastatic Transitional cell carcinoma of the urothelium (TCCU) who achieved disease control (i.e. CR, PR or SD) after four cycles of first line standard doublet chemotherapy regimen with Gemcitabine-Cisplatin (GC).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization- Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. The study was conducted in compliance with the protocol. The protocol, amendments, and the subject informed consent received Institutional Review Board (IRB)/Independent Ethics Committee IEC) approval/favourable opinion prior to initiation of the study and/or their implementation. Freely given written informed consent was to be obtained from every subject or his or her legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

Background therapy:

Standard anti-emetic prophylaxis was recommended from the first cycle, prior to each treatment administration of vinflunine IV infusion and consisted of a single oral dose of dexamethasone 8 mg or equivalent dose of methylprednisolone.
Laxatives and dietary measures were recommended, starting from day 1 of each vinflunine administration to day 5.
For patients considered at increased risk of serious constipation, defined as history of chronic or refractory constipation, concomitant treatment with opioids, peritoneal carcinomatosis or abdominal tumour masses, persistent symptoms under vinflunine despite the days 1 to 5 dietary measures and laxatives administration, the use of a stool softener and a stimulant was recommended to maximise efficacy.

Evidence for comparator:

The study was a non comparative, single arm, phase II trial as it aimed at evaluating the efficacy of single agent VFL as Maintenance Therapy following standard chemotherapy regimen by Gemcitabine-cisplatin (GC) combination regimen. Vinflunine is already approved as monotherapy in second line for patients with advanced/metastatic TCCU.

Actual start date of recruitment	30 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	28 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 14

Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between February 17th 2012 and July 24th 2013, a total of 20 patients with advanced or metastatic TCCU were registered at 11 investigational centres in Germany, Austria and Italy. 1 patient was withdrawn from study before first drug administration, he was considered as screen failure.

Pre-assignment

Screening details:

Treatment with GC chemotherapy was not part of this study. Inclusion into the trial had to take place only after completion of the 4 cycles of GC treatment. Only patients who achieved a complete response (CR), a Partial response (PR) or a stable disease (SD) after the 4 cycles of GC therapy were eligible to enter into the study to receive IV VFL.

Period 1

Period 1 title	Maintenance treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Vinflunine arm

Arm description:

The study population was patients aged ≥ 18 years with advanced or metastatic TCCU, who achieved disease control (CR, PR or SD) after four cycles of first line chemotherapy regimen with GC treatment.

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	
Other name	Vinflunine ditartrate, Javlor
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug administration had to start within 7 days after registration. Vinflunine was administered on Day 1, every 21 days as a 20 minute intravenous (IV) infusion.
For cycle 1, the starting dose of vinflunine was defined according to calculated creatinine clearance at registration (Cockroft-Gault formula), age, ECOG PS and prior pelvic irradiation. The treatment with vinflunine as MT was to be administered until documented disease progression, unacceptable toxicity, intercurrent illness or other reaction which could require discontinuation of study drug or patient refusal. As per the VFL Summary of Product Characteristics (SmPC), the recommended dose of VFL as single agent is 320 mg/m² as a 20 minute intravenous infusion every 3 weeks in patient without renal impairment (CrCl > 60 mL/mn) and 280 mg/m2 in patients with an ECOG PS of 1 or 0 with prior pelvic irradiation. In case of documented progression occurring before the first evaluation, the treatment was discontinued.

Number of subjects in period 1	Vinflunine arm
Started	19
Completed	0
Not completed	19
Drug related toxicity	2
Physician decision	1
Non-drug related toxicity	1

Patient's refusal/convenience	8
Progression Disease	6
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Vinflunine arm

Reporting group description:

The study population was patients aged ≥ 18 years with advanced or metastatic TCCU, who achieved disease control (CR, PR or SD) after four cycles of first line chemotherapy regimen with GC treatment.

Reporting group values	Vinflunine arm	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous Units: years			
median	67.2		
full range (min-max)	48.9 to 77.4	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	13	13	
ECOG PS Units: Subjects			
Zero	11	11	
One	8	8	
Primary tumour site Units: Subjects			
Upper urinary tract	2	2	
Bladder	17	17	
Body surface area (BSA) Units: square meter			
arithmetic mean	1.9		
standard deviation	± 0.2	-	

End points

End points reporting groups

Reporting group title	Vinflunine arm

Reporting group description:

The study population was patients aged ≥ 18 years with advanced or metastatic TCCU, who achieved disease control (CR, PR or SD) after four cycles of first line chemotherapy regimen with GC treatment.

Primary: PFS Rate at 3 months

End point title	PFS Rate at 3 months[1]

End point description:

As exploratory analysis, the primary efficacy endpoint was analysed on the first 20 patients included before termination of the study, that is to say, on the 19 patients, representing the ITT population and on the 15 evaluable patients for response.

End point type	Primary

End point timeframe:

The primary efficacy parameter was the PFS rate at the fixed time point of 3 months after registration into the study. The PFS Rate has been estimated using Kaplan Meier Method.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to early study termination, the analysis of the primary efficacy endpoint on the first 20 evaluable patients and on the total and required number of 70 evaluable patients for the second step Fleming design could not be performed.

End point values	Vinflunine arm			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage	82			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AE occurring during the study period (starting after the first dose of medication and up to and including 30 days after the last dose of medication),spontaneously reported by the patient or observed by others was recorded.

Adverse event reporting additional description:

Each patient was assessed for occurrence of adverse events throughout the study period. Adverse events were graded according to NCI- CTC AE criteria
The adverse events as well as baseline signs and symptoms were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Treated patients

Reporting group description: -

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm	Additional description: Grade 4		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Fatigue	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Eye disorders			
Visual acuity reduced	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure	Additional description: Grade 5		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Ureteric fistula	Additional description: Grade 1		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection	Additional description: Grade 3		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.7 %

Non-serious adverse events	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	25		
Infusion site pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	4		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Investigations			
Glomerular filtration rate			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypertonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	6		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	9		
Blood and lymphatic system disorders			

Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Neutropenia subjects affected / exposed occurrences (all)	14 / 19 (73.68%) 76		
Anaemia subjects affected / exposed occurrences (all)	18 / 19 (94.74%) 99		
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 19 (31.58%) 18		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 4		
Tinnitus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 4		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3		
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 4		
Constipation subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 5		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 15		
Dyspepsia			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3		
Nausea subjects affected / exposed occurrences (all)	7 / 19 (36.84%) 16		
Stomatitis subjects affected / exposed occurrences (all)	5 / 19 (26.32%) 18		
Vomiting subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 7		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	7 / 19 (36.84%) 23		
Renal and urinary disorders Bladder pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2		
Infections and infestations Herpes zoster subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 4		
Hypokalaemia			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	Study becoming an European study (Austria, Germany, Italy...) with updating number of centres involved. Including an update of the prohibited and non-recommended concomitant treatments regarding the use of dexamethasone as anti-emesis prophylaxis in the study. Including an update of Vinflunine IV Summary of product characteristics and Investigator's brochure. Including an update of registration form.
14 May 2012	Local requirement of performing monthly pregnancy test for women of childbearing potential during the treatment phase of patients included.
25 June 2012	Change of study selection criteria and the registration form (to involve patients > 75 years with dose adaptation, to other one additional week to complete the patients baseline clinical assessments, to adapt one exclusion criterion related to other malignancies + a cut-off value for haemoglobin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to difficulties in recruiting patients, the decision to stop the study before the first interim analysis was taken by the sponsor in agreement with the investigators. The study population consisted of 20 patients included, of whom 19 were treated

Notes: