

**Clinical trial results:****Randomized phase III study comparing vinflunine-gemcitabine and gemcitabine-carboplatin combinations in patients ineligible to cisplatin with advanced or metastatic urothelial carcinoma.****Summary**

EudraCT number	2014-005396-82
Trial protocol	ES FR PL CZ AT GB BE IT
Global end of trial date	08 January 2017

Results information

Result version number	v1 (current)
This version publication date	22 November 2018
First version publication date	22 November 2018

Trial information**Trial identification**

Sponsor protocol code	L00070IN312P1
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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, F 92100
Public contact	Responsable ensayos clínicos intern, Pierre Fabre Ibérica, S. A., 34 934833049, anabelen.paules@pierre-fabre.es
Scientific contact	Responsable ensayos clínicos intern, Pierre Fabre Ibérica, S. A., 34 934833049, anabelen.paules@pierre-fabre.es

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	23 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the median Progression Free Survival without related Severe Acute Toxicity* between arms (called SAT-PFS).

*[enlarged definition of the Severe Acute Toxicity (SAT) from the EORTC study 30986 adding vinflunine specific risks: neutropenia G4 > 7 days, neutropenic fever G3/4, neutropenic systemic sepsis G3/G4 (neutropenia G3/4), G3/G4 thrombocytopenia with bleeding, G3/4 renal toxicity, G3/4 mucositis, constipation G4 requiring surgery, and death].

Protection of trial subjects:

A Data Monitoring Committee (DMC) was to be convened to review all the safety and efficacy data and make recommendations regarding the decision to stop or continue the trial after the interim analysis

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	2
EEA total number of subjects	0

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)	1
From 65 to 84 years	1

Subject disposition

Recruitment

Recruitment details:

Only 2 patients were included and treated in 2 centres in Taiwan. Due to delay in implementing the study across Europe and the difficulties to include patients in Taiwan, the Sponsor has decided on 26/Jun/2016 to stop the recruitment of patients in Taiwan and in July 2016 not to initiate the study in Europe.

Pre-assignment

Screening details:

A total of 4 patients with a confirmed diagnosis of locally advanced or metastatic predominantly transitional cell carcinoma of the urothelium (TCCU) [were screened in Taiwan, two were screen failures and 2 were eligible to participate to the study and were randomized into the study on 22/Feb/2016 and 28/Mar/2016, respectively in 2 sites in Taiwan

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm VG

Arm description:

vinflunine plus gemcitabine

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	L0070
Other name	Javlor
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

administered on Day (D) 1, every 21 days as a 20-minute IV infusion with two starting dose options based on randomization calculated creatinine clearance by Cockcroft-Gault formula (CrCl),
- CrCl \geq 40 mL/min: 280 mg/m²; in case of significant* haematological or non-haematological toxicity, dose reduced to 250 mg/m².
- CrCl < 40 mL/min (but \geq 30): 250 mg/m²; in case of significant* haematological or non-haematological toxicity, dose reduced to 225 mg/m².

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	GEM
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (GEM): administered on D1 and 8 of every 21-day cycle as a 30-minute IV infusion, Starting dose at 750 mg/m² on D1 and 8 during the first cycle, escalated to 1000 mg/m² if no toxicity of Grade > 2 occurs in Cycle 1, and pursued on the same dose in the absence of significant haematological or non-haematological toxicity and if CrCl \geq 30 mL/min

Arm title	Arm GC
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Arm description:

Gemcitabine (GEM): administered on D1 and 8 of every 21-day cycle as a 30minute IV infusion, Starting dose at 1000 mg/m² and pursued on the same dose in the absence significant haematological or non-haematological toxicity
Carboplatin (CBDCA): administered on D1 of every 21- day cycle as a 60 minutes IV infusion: AUC 4.5

(Calvert dose calculation formula) and pursued on the same dose in the absence of significant haematological or non-haematological toxicity

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	GEM
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

administered on D1 and 8 of every 21-day cycle as a 30minute IV infusion, Starting dose at 1000 mg/m² and pursued on the same dose in the absence significant haematological or non-haematological toxicity

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	CBDCA
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

administered on D1 of every 21- day cycle as a 60 minutes IV infusion: AUC 4.5 (Calvert dose calculation formula) and pursued on the same dose in the absence of significant haematological or non-haematological toxicity

Number of subjects in period 1	Arm VG	Arm GC
Started	1	1
Completed	0	0
Not completed	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Arm VG
Reporting group description: vinflunine plus gemcitabine	
Reporting group title	Arm GC
Reporting group description: Gemcitabine (GEM): administered on D1 and 8 of every 21-day cycle as a 30minute IV infusion, Starting dose at 1000 mg/m ² and pursued on the same dose in the absence significant haematological or non-haematological toxicity Carboplatin (CBDCA): administered on D1 of every 21- day cycle as a 60 minutes IV infusion: AUC 4.5 (Calvert dose calculation formula) and pursued on the same dose in the absence of significant haematological or non-haematological toxicity	

Reporting group values	Arm VG	Arm GC	Total
Number of subjects	1	1	2
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	1	1
From 65-84 years	1	0	1
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	1	1	2
Performance status			
ECOG status			
Units: Subjects			
ECOG 0	0	1	1
ECOG 1	1	0	1

End points

End points reporting groups

Reporting group title	Arm VG
Reporting group description:	
vinflunine plus gemcitabine	
Reporting group title	Arm GC
Reporting group description:	
Gemcitabine (GEM): administered on D1 and 8 of every 21-day cycle as a 30minute IV infusion, Starting dose at 1000 mg/m ² and pursued on the same dose in the absence significant haematological or non-haematological toxicity	
Carboplatin (CBDCA): administered on D1 of every 21- day cycle as a 60 minutes IV infusion: AUC 4.5 (Calvert dose calculation formula) and pursued on the same dose in the absence of significant haematological or non-haematological toxicity	

Primary: Progression Free Survival

End point title	Progression Free Survival ^[1]
End point description:	
due to premature global end of trial as per amendment 02, Due to the low number of patients and according to clinical study protocol amendment PA02, no statistical analyses were performed, only the individual data collected of the 2 enrolled patients are provided by listings for efficacy and safety analyses.	
End point type	Primary
End point timeframe:	
Each patient had to receive at least 2 cycles of study treatment until documented disease progression, unacceptable toxicity or patient refusal. Tumour response was assessed every 6 weeks according to RECIST guidelines	

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 premature end of trial with only two patients enrolled and treated; no formal statistical analysis was performed

End point values	Arm VG	Arm GC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: month				
median (full range (min-max))	10 (10 to 10.2)	4 (4 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse or inter-current event occurring during the study period (starting after the first dose of study medication and up to and including 30 days after the last dose of study medication).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Arm VG
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Reporting group description:
vinflunine plus gemcitabine

Reporting group title	Arm GC
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Reporting group description:

Gemcitabine (GEM): administered on D1 and 8 of every 21-day cycle as a 30minute IV infusion, Starting dose at 1000 mg/m² and pursued on the same dose in the absence significant haematological or non-haematological toxicity

Carboplatin (CBDCA): administered on D1 of every 21- day cycle as a 60 minutes IV infusion: AUC 4.5 (Calvert dose calculation formula) and pursued on the same dose in the absence of significant haematological or non-haematological toxicity

Serious adverse events	Arm VG	Arm GC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Hyponatraemia	Additional description: grade 2 hyponatraemia occurred during cycle 1 , was treated by an intravenous solution of sodium chloride 3%. It did not result in any change in the study medications and resolved during cycle 2.		
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm VG	Arm GC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
Blood and lymphatic system disorders			

Neutropenia	Additional description: the patient treated in arm VG, experienced mainly neutropenia with Grade 3 intensity (n=7), none of them was considered as serious by the investigator and all episodes resolved.		
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	7	0	
Thrombocytopenia	Additional description: For pt treated in arm GC, related adverse events were in the haematological SOC consisting thrombocytopenia, with one episode of grade 4 at Cycle 3 resulting in treatment discontinuation.		
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pyrexia	Additional description: grade 1 pyrexia that occurred at cycle 1 and was not related		
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
decrease appetite			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Hiccups			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders			
Adrenal insufficiency	Additional description: not related event that occurred at cycle 1 and was still on going		
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2015	Protocol Amendment N°1: general (i.e. applicable for countries), – substantial, was issued on 12-Nov-2015. The following changes were include - Allow the supply of Gemcitabine concentrate for solution for infusion. - Corrections of typing errors with regards to the Creatinine Clearance assessment in the Study flow chart, the pharmaceutical form, storage and labelling of Carboplatin. - Update of Sponsor’s personnel
21 September 2016	Protocol Amendement 02 Local, applicable for TAIWAN only, substantial, The following changes were included: - Modification of the end of study definition - Update of the Sponsor’s personnel list. Due to the low number of patients and according to clinical study protocol amendment PA02, no statistical analyses were performed, only the individual data collected of the 2 enrolled patients are provided by listings for efficacy and safety analyses.

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 the low number of patients and according to clinical study protocol amendment PA02, no statistical analyses were performed, only the individual data collected of the 2 enrolled patients are provided by listings for efficacy and safety analyses

Notes: