Clinical trial results:
Phase II single-arm study of first line treatment with gemcitabine and pazopanib in patients with inoperable locally advanced or metastatic biliary tree cancer (cholangiocarcinoma or gallbladder carcinoma)

Summary

EudraCT number	2012-001705-24
Trial protocol	GR
Global end of trial date	28 September 2018

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019

Trial information

Trial identification

Sponsor protocol code	HE37/12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01855724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	M. Hatzikostanti 18, Athens, Greece, 11524
Public contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr

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 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of pazopanib combination with gemcitabine (measured as Objective Response Rate) in patients with inoperable locally advanced or metastatic biliary tree carcinoma.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines and the local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	10
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 28 June 2013 until 15 March 2018 from 10 sites in Greece.

Pre-assignment

Screening details:

Patients were screened for eligibility before entering the study and signed the informed consent form which was obtained before any study procedure.

Period 1

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

Arms

Arm title	Gemcitabine - Pazopanib

Arm description:

Gemcitabine (1000mg/m2, D1 & 8) - Pazopanib (800mg daily dose) treatment combination was administered in treatment cycles, of 21 day duration per cycle. In the absence of disease progression or significant toxicity, 8 cycles of combination treatment were administered, followed by Pazopanib monotherapy at an 800 mg daily dose. Following 8 cycles of Gemcitabine – Pazopanib treatment, patients continued with Pazopanib monotherapy. Each monotherapy cycle had duration of 21 days. Patients received 800mg Pazopanib orally on a daily basis until disease progression or toxicity that was treated and significantly affected their QoL

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cytotoxic agent Gemcitabine, was administered at an 1000 mg/m2 dose diluted in 250 ml of N/S, in a 30-minute intravenous infusion on days 1 and 8, every 21 days, for 8 cycles.

Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib was administered at the dose of 800mg on daily basis for 8 cycles of 21 days duration. In the absence of disease progression or significant toxicity Pazopanib was administered as maintenance treatment (monotherapy) at an 800mg daily dose.

Number of subjects in period 1	Gemcitabine - Pazopanib
Started	29
Completed	11
Not completed	18
Physician decision	1
Consent withdrawn by subject	2
Disease progression	7
Adverse event, non-fatal	6
Death	1
Temporary suspension of the trial	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	29	29	
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	
From 65-84 years	18	18	
85 years and over	1	1	
Age continuous Units: years			
median	68.6		
full range (min-max)	46.5 to 85.0	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	15	15	

Subject analysis sets

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients who received at least one full study medication cycle, had an initial disease evaluation and the right histological type of cancer.

Reporting group values	Per Protocol Population		
Number of subjects	21		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	13		
85 years and over	1		
Age continuous Units: years			
median	68.6		
full range (min-max)	46.5 to 85.0		
Gender categorical Units: Subjects			
Female	11		
Male	10		

End points

End points reporting groups

Reporting group title	Gemcitabine - Pazopanib

Reporting group description:

Gemcitabine (1000mg/m2, D1 & 8) - Pazopanib (800mg daily dose) treatment combination was administered in treatment cycles, of 21 day duration per cycle. In the absence of disease progression or significant toxicity, 8 cycles of combination treatment were administered, followed by Pazopanib monotherapy at an 800 mg daily dose. Following 8 cycles of Gemcitabine – Pazopanib treatment, patients continued with Pazopanib monotherapy. Each monotherapy cycle had duration of 21 days. Patients received 800mg Pazopanib orally on a daily basis until disease progression or toxicity that was treated and significantly affected their QoL

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients who received at least one full study medication cycle, had an initial disease evaluation and the right histological type of cancer.

Primary: Objective response Rate

End point title	Objective response Rate[1]

End point description:

Objective response rate was defined as the percentage of patients with a confirmed complete (CR) or partial response (PR) as per RECIST 1.1 criteria.

End point type	Primary

End point timeframe:

Imaging evaluation for the determination of tumor response was performed every 8 weeks.

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: The objective response rate, i.e. the percentage of patients achieving a complete or partial response as the best response was described using descriptive statistics for the ITT and the PP population

End point values	Gemcitabine - Pazopanib	Per Protocol Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	21		
Units: percentage of patients with CR/PR				
Objective response rate (%)	14	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression Free Survival was calculated from the date of patient's entry into the study until the first documented disease progression, death or last contact, whichever occurred first.

End point type	Secondary

End point timeframe:

Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8).

End point values	Gemcitabine - Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: months				
median (confidence interval 95%)	6.3 (2.3 to 8.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival was calculated from the date of patient's entry into the study until death or last contact.

End point type	Secondary

End point timeframe:

Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8).

End point values	Gemcitabine - Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: months				
median (confidence interval 95%)	10.4 (7.3 to 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Safety was assessed in the safety population consisting of all patients that received at least one dose of the study drug (s).

End point type	Secondary

End point timeframe:

Evaluation of Adverse Events (AEs) was performed every 21 days (per treatment cycle) throughout the course of treatment.

End point values	Gemcitabine - Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: number of patients				
Any adverse event	29			
Fatal adverse event	1			
Serious adverse event	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

The Quality of Life (QoL) was assessed using the EUROQOL 5D questionnaire that consists of 5 dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ-VAS measuring the patient's health status in a scale of 0 to 100 with 0 indicating the worst health and 100 corresponding to the best health, as rated by the patient.

End point type	Secondary

End point timeframe:

The EUROQOL 5D Questionnaire was completed before treatment initiation, every 8 weeks and post treatment.

End point values	Gemcitabine - Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	28[2]			
Units: EQ-VAS				
arithmetic mean (standard deviation)				
Baseline	55 (± 31.3)			
Last treatment cycle	54.1 (± 30.2)			

Notes:

[2] - 28 patients completed the EQ-5D questionnaire at baseline and 23 at their last cycle of treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month Progression Free Survival Rate

End point title	6-month Progression Free Survival Rate

End point description:

The percentage of patients surviving 6 months post study entry.

End point type	Secondary

End point timeframe:

Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8).

End point values	Gemcitabine - Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percentage of patients	52			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Upon signature of the ICF up to 30 days after the last administration of Pazopanib. Following the 30 day EOT visit all ongoing SAEs as well as ongoing related AEs and new related SAEs were collected and followed till resolution/stabilisation/new treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Gemcitabine - Pazopanib

Reporting group description:

The combination was administered as follows: Gemcitabine 1000mg/m2 i.v on days 1 and 8 with Pazopanib 800mg daily dose per os on days 1-21, every 21 days for 8 cycles followed by Pazopanib monotherapy 800mg daily dose per os in days 1-21 every 21 days until disease progression was occurred or unacceptable toxicity.

Serious adverse events	Gemcitabine - Pazopanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 29 (44.83%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Alkaline Phosphatase increased	Additional description: increased level of alkaline phosphatase in a blood specimen		

subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ischaemic stroke				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
jejunal hemorrhage	Additional description: Bleeding from the jejunal wall.			
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Lung abscess			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hepatic coma			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic infection			
subjects affected / exposed	1 / 29 (3.45%)		
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 %

Non-serious adverse events	Gemcitabine - Pazopanib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 29 (51.72%)		
occurrences (all)	32		
General disorders and administration site conditions			
edema face			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
edema limbs			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	16 / 29 (55.17%)		
occurrences (all)	21		
fever			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	6		
other - voice disorders			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Cough			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
other - pharyngolaryngeal pain			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
other - distress			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Investigations			
White blood cell count decreased			
subjects affected / exposed	24 / 29 (82.76%)		
occurrences (all)	79		
Neutrophil count decreased			
subjects affected / exposed	24 / 29 (82.76%)		
occurrences (all)	71		
Alanine aminotransferase increased			
subjects affected / exposed	15 / 29 (51.72%)		
occurrences (all)	32		
alkaline phosphatase increased			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	11		
Aspartate aminotransferase increased			

subjects affected / exposed	13 / 29 (44.83%)		
occurrences (all)	22		
Blood bilirubin increased			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	13		
cholesterol high			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	5		
creatinine increased			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	10		
other - lactate dehydrogenase serum increased			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	11		
Platelet count decreased			
subjects affected / exposed	12 / 29 (41.38%)		
occurrences (all)	30		
Amylase increased			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Sinus tachycardia			

subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all)	 2 / 29 (6.90%) 3 2 / 29 (6.90%) 3 1 / 29 (3.45%) 1 1 / 29 (3.45%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 12 / 29 (41.38%) 17		
Eye disorders other - eyelash oedema alternative dictionary used: CTCAE 4.03 subjects affected / exposed occurrences (all) watering eye alternative dictionary used: CTCAE 4.03 subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 2 1 / 29 (3.45%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Constipation	 7 / 29 (24.14%) 12 1 / 29 (3.45%) 1		

subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	8 / 29 (27.59%)			
occurrences (all)	14			
Dyspepsia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Oesophageal haemorrhage				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Reflux gastritis				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Haematochezia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
other - epigastric pain				
alternative dictionary used: CTCAE 4.03				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
other - mucosal defecation				
alternative dictionary used: CTCAE 4.03				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences (all)	3			
Nausea				
subjects affected / exposed	8 / 29 (27.59%)			
occurrences (all)	13			
Periodontal disease				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Vomiting				

subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Acne			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Hair colour changes			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Skin hyperpigmentation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	8		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		

Back pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Infections and infestations			
Cholangitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Papulopustular rash			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
other - anorexia			
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	5		
Hyperglycaemia			

subjects affected / exposed	6 / 29 (20.69%)			
occurrences (all)	16			
Hyperkalaemia				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Hypermagnesaemia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Hypernatraemia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Hypertriglyceridaemia				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Hypoalbuminaemia				
subjects affected / exposed	5 / 29 (17.24%)			
occurrences (all)	7			
Hypocalcaemia				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	6			
Hypoglycaemia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	1			
Hypokalaemia				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	7			
Hypomagnesaemia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences (all)	4			
Hyponatraemia				
subjects affected / exposed	6 / 29 (20.69%)			
occurrences (all)	7			
Hypophosphataemia				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Hyperphosphataemia				

subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	Amendment of the inclusion criteria 3 and 6: Criterion 3: Histologic or cytologic diagnosis of cholangiocarcinoma (intrahepatic or extrahepatic biliary adenocarcinoma, gallbladder adenocarcinoma and periampullary bile duct adenocarcinoma). Criterion 6: No previous administration of other chemotherapy or targeted therapy. By exception, patients with primary lesion that was removed in the past and received adjuvant chemotherapy with gemcitabine, with the last dose being administered at least 1 year prior the patient's inclusion date in this protocol, are acceptable. Pages 23-25: Pazopanib (Votrient®) available for the study from its initiation onwards is available in white 200mg tablets (34 in each bottle) compared to the pink, commercially available, tablets. The stock for this IMP expires in November 2017 and will be used to cover the needs of the study patients until stock-out and as per its expiry date. Then, pazopanib (Votrient®) supplied in the study, will be the 200mg commercially available product (pink tablets, 90 in each bottle), in its commercial packaging with appropriate labelling for use in the clinical trial. Packaging and labelling of the commercially available medicinal product to be used in the clinical trial will be performed by Novartis as per GMP, ICH/GCP and local law requirements. Labels will include the necessary information in Greek, will comply with applicable legislation and will not provide any patient information. Pazopanib will be dispensed to patients for home use at each study visit from the study physician/designated site personnel. Each package will contain sufficient drug supply until the patient's next visit. Study drug will be received by a delegated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and delegated site personnel have access. Upon receipt, pazopanib should be stored according to the instructions on the drug label.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 July 2013	For safety reasons, upon a request from Glaxo Smith Kline, in clinical studies investigating the combination of Gemcitabine – Pazopanib the enrollment was suspended.	05 May 2014

Notes:

Limitations and caveats

None reported