Clinical trial results:
HYPAZ: An open-label investigation into hypertension induced by pazopanib therapy

Summary

EudraCT number	2010-021613-23
Trial protocol	GB
Global end of trial date	25 September 2014

Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016
Summary attachment (see zip file)	HYPAZ AE Listing and Frequency Table (HYPAZ AE Listing and Frequency table for Eudract.pdf)

Trial information

Trial identification

Sponsor protocol code	A091962

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01392352
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust & University of Cambridge
Sponsor organisation address	Addenbrooke’s Hospital, Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Chief Investigator, Cambridge University Hospitals NHS Foundation Trust , cctu.cancer@addenbrookes.nhs.uk
Scientific contact	Chief Investigator, Cambridge University Hospitals NHS Foundation Trust , cctu.cancer@addenbrookes.nhs.uk

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	17 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2014
Global end of trial reached?	Yes
Global end of trial date	25 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

What causes high blood pressure in some patients taking pazopanib as a treatment for cancer?

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Authority. Patients received verbal and written information prior to consenting to the trial and had the time to consider their participation and opportunity to ask questions. Consenting patients had a series of screening tests and exams to ensure they were suitable for the study and that it was safe to proceed. The patients were monitored in the clinic every 2 weeks up to 12 weeks for assessment and monitoring of safety including ECG, Vital signs, blood/ urine tests. A visit at 3 weeks of treatment was added partway through the trial to monitor liver function. CT scans were performed at 12 weekly intervals to monitor disease status. After 12 weeks, patients who continued treatment were then monitored every 4 weeks up to 6 months, then every 3 months Treatment was stopped or dose reduced on the development of treatment toxicities. Patients received pazopanib therapy until death, loss of clinical benefit, unacceptable toxicity or withdrawal from the study for any other reason. Patients attended a follow-up visit 28 days after stopping pazopanib therapy for safety and disease status assessments. On registration to the trial, the patients were allocated a unique reference number to be used on all data and samples sent to the Sponsor which allowed their personal data to remain anonymous. Only the patients' direct care team had access to their recruited participants personal data during the study. Patients were allowed to withdraw their consent to the study at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2011
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	United Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	18
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was open to recruitment on 20-Jan-2011. The 1st patient was recruited on 23-Jun-2011 and the last patient was recruited on 04-Jul-2014. Potential patients were identified at routine outpatient clinics by their oncologist and those interested were referred to the Phase 1 clinic for discussion of clinical trials (including HYPAZ).

Pre-assignment

Screening details:

95 patients given information, 53 consented, 31 patients were eligible for the trial following a 28 day screening period. 4 patients did not receive Pazopanib treatment since they failed the eligibility criteria at the baseline visit prior to treatment.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Patients

Arm description: -

Arm type	All Patients Taking IMP
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	GW786034
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg once daily

Number of subjects in period 1	All Patients
Started	27
Completed	27

Period 2

Period 2 title	Hypertension Visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Hypertensive Group
Arm description: -	
Arm type	Observational Grouping
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	GW786034
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 800 mg once daily	
Arm title	Non Hypertensive
Arm description: -	
Arm type	Observation Grouping
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	GW786034
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 800 mg once daily	

Number of subjects in period 2	Hypertensive Group	Non Hypertensive
Started	3	24
Completed	3	10
Not completed	0	14
Lost to follow-up	-	14

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	59.5		
standard deviation	± 12.6	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	10	10	

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description: -	
Reporting group title	Hypertensive Group
Reporting group description: -	
Reporting group title	Non Hypertensive
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who receive at least one dose of pazopanib will be included in the safety population.	
Subject analysis set title	Research Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who complete visit V2, or V8/VHyp (as applicable) will be included in the research population. This population will be used in evaluation of the primary and secondary endpoints.	

Primary: forearm blood flow ratio

End point title	forearm blood flow ratio
End point description:	
Change in forearm blood flow ratio (of infused vs control arm) in response to intra-arterial acetycholine infusion. There is a hierarchy of observations: Patient, Visits (baseline and Hyp), Dose (Saline or active Challenge Dose), forearm (control or infused), and replications of individual forearm blood flow observations (3-4). Aggregate endpoints for each patient are calculated that are the ratio of ratios of geometric means of individual Infused:Control forearm ratios: (Challenge / Saline at Visit Hyp)/ (Challenge/ Saline at Baseline).	
End point type	Primary
End point timeframe:	
measured at initial baseline visit, and subsequent visit where a patient was classified as either hyper-tensive or non-hyper-tensive according to blood pressure measurements.	

End point values	Hypertensive Group	Non Hypertensive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	10		
Units: unit-less ratio				
arithmetic mean (standard deviation)	1.55 (± 0.37)	3.7 (± 2.22)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
A mixed effect model was used to predict the log-transformed infused:control forearm blood flow ratio values as a function of Visit, Dose, Hypertensive status. Random effect intercepts were fitted at the	

patient and patient-visit level.

They key estimate for the scientific interpretation is the interaction between (Visit Hyp – Visit baseline):(High Dose – Base Dose):(Hypertension – non-Hypertension), which corresponds to the study objectives.

Comparison groups	Hypertensive Group v Non Hypertensive
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6527
Method	Mixed models analysis
Parameter estimate	log difference
Point estimate	-0.0854
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4604
upper limit	0.2927
Variability estimate	Standard error of the mean
Dispersion value	0.189

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from screening through to the follow-up visit, 28 days post last dose of pazopanib.

Adverse event reporting additional description:

Adverse events were assessed at each clinic visit throughout the study by a clinician.

A document listing the individual Adverse Events, and providing a frequency table broken down by AE category, grade, relatedness, and seriousness, is uploaded separately.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3

Reporting groups

Reporting group title	All Patients

Reporting group description: -

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 27 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thromboembolic Event			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 11			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Shortness of breath			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureteric obstruction			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
alternative dictionary used: MedDRA 11			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
alternative dictionary used: MedDRA 11			

subjects affected / exposed	1 / 27 (3.70%)		
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	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)		
General disorders and administration site conditions			
Adverse event	Additional description: One patient received 4 days of pazopanib treatment, stopped treatment due to patient choice and did not return for follow-up. No AEs were reported for this patient as lost to follow-up.		
subjects affected / exposed	26 / 27 (96.30%)		
occurrences (all)	327		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2010	Substantial amendment to protocol, PIS to include requirement for male participant contraception. Amendment was part of initial application to REC and was submitted to the MHRA only.
08 March 2011	Substantial amendment to expanding patient population. Changes made to protocol and patient documents.
14 March 2012	Substantial amendment to expand patient population; change to primary endpoint definition; Increase to screening visit window for scheduling; changes to inclusion and exclusion criteria to aid recruitment; MRI exclusions modified to allow patients with non-measurable lesions to still have this test; Information sheet: visit windows modified to reflect new protocol. Time of video imaging changed to truly reflect the actual time it takes (longer than previously anticipated.
13 July 2012	Substantial amendment to MHRA only: Change of drug supplier from Aptuit to Catalent (administrative take-over).
06 February 2013	Substantial amendment to Expand patient population to aid recruitment & Update of safety information. The main changes to the protocol were: -Changes to the inclusion/exclusion criteria to allow patients who have received prior TKI/antiangiogenic treatments to participate (with a wash-out period of 12 weeks) -Removal of exclusion criteria Diabetes, on oral therapy/insulin -Exclusion criteria 3: Time limit added to history of certain cardiovascular conditions (within 6 months) -Clarification of definition of endobronchial lesions or lesions infiltrating major pulmonary vessels -Addition of 24-hour urine collection at Visits 2/3/8/VHyp for urine sodium measurement -Window for screening DCE-MRI scans increased to 14 days prior to V2 (interval between 2 scans remains the same) -Addition of safety information from the GSK sarcoma trials -Minor changes and corrections were made throughout the protocol. The main changes to the participant information sheet were: -Addition of information as a result of the sarcoma indication. -Addition of 24-hour urine collection information in the flowsheets.
10 January 2014	Substantial amendment to protocol and PIS: Timing of interim analysis changed from 36 patients to 10 with changes to DMC sections also. Addition of Visit 3b to add liver monitoring tests (due to emerging safety). Addition of Thyroid function tests at Day 28 and day 56 (due to emerging safety). Change to CTA- change from study-specific supply to commercial supply with resulting changes in protocol and CTA. PIS: addition of extra visit, update to safety information, addition of paragraph to warn of change in appearance of study medication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported