



Clinical trial results:

A phase II study of pazopanib in patients with metastatic or unresectable renal cell carcinoma (RCC) who have failed prior sunitinib therapy

Summary

EudraCT number	2010-022770-13
Trial protocol	IE SE
Global end of trial date	15 July 2020

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	ICORG 10-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01566747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	Ardilaun House, St Stephens Green, Ireland, D02 VN51
Public contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie

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	01 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2020
Global end of trial reached?	Yes
Global end of trial date	15 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to assess the progression free rate at 4 months (i.e. completion of 4 months of treatment, with no disease progression at 8 weeks, and no evidence to suggest disease progression before the 4 month time-point).

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and Cork Teaching Hospitals Clinical Research Ethics Committee on 12th Jan 2011.

Background therapy:

N/A all patients will receive Pazopanib. Patient must have also received prior treatment with sunitinib for at least 12 weeks in order to participate in this study. Prior treatment with either temsirolimus or everolimus will also be allowed as these treatments have been proven to be effective as 2nd line therapy of RCC.

Evidence for comparator:

The aim of this study is to assess the efficacy of pazopanib in treating patients with metastatic renal cell carcinoma whose cancer has progressed following treatment with sunitinib. As there are currently a number of small molecules approved in the RCC setting, major interest now lies in defining the best sequence of drugs and whether persistent targeting of the VEGF receptor family is warranted following failure of a prior VEGF directed therapy. Sunitinib is a multi-kinase inhibitor of VEGFR 1, VEGFR 2, VEGFR 3, PDGFR α/β , c kit, Flt-3, CSF-1 and RET while pazopanib is a selective inhibitor of VEGFR 1, 2, 3, PDGFR α/β and c kit. This study aims to assess if pazopanib retains activity against the RCC following progression on sunitinib therapy with the biological rationale being that the non-overlapping targets may confer different activity levels.

Actual start date of recruitment	08 March 2011
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	Sweden: 3
Country: Number of subjects enrolled	Ireland: 51
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	36
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

54 patients were consented from 8 sites in Ireland and Sweden from 08-Mar-2011 until 05-Feb-2016

Pre-assignment

Screening details:

The target population for this study was patients with metastatic or unresectable renal cell carcinoma, who had been previously treated with sunitinib and relapsed. The patients had to meet all other inclusion criteria and none of the exclusion criteria.

Period 1

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

Blinding implementation details:

N/A As Blinding Not Used for Study.

Arms

Arm title	Single Arm
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Arm description:

Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib in patients with metastatic or unresectable RCC

Arm type	Experimental
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:

Pazopanib 800mg day to be given continuously until disease progression unacceptable toxicity or withdrawal of consent.

Pazopanib monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200mg and 400mg of the freebase:

- 200mg, oval-shaped, white, packaged in bottles containing 34 tablets each
- 400mg, oval-shaped, white, packaged in bottles containing 68 tablets each

Starting on Day 1 of the Treatment Period, each subject will receive 800mg (2 X 400mg tablets) of pazopanib to be administered once daily by mouth. The 200mg tablets of pazopanib will be provided to subjects who need dose adjustments during the study

Response assessments were to be carried out every 8 weeks for the first 24 weeks (six months) and then every twelve weeks until disease progression. Safety assessments were to be carried out every 4 weeks for the first six months and then every eight weeks until disease progression.

Number of subjects in period 1	Single Arm
Started	54
Completed	4
Not completed	50
Adverse event, serious fatal	47
Consent withdrawn by subject	1

Study Closure	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Single Arm
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Reporting group description: -

Reporting group values	Single Arm	Total	
Number of subjects	54	54	
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	36	36	
85 years and over	0	0	
Age continuous			
Units: years			
median	58.5		
full range (min-max)	40 to 81	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	41	41	
Race			
Units: Subjects			
Caucasian	54	54	
Height at creening (cm)			
Units: cm			
median	174		
full range (min-max)	148 to 194	-	
Weight at Screening			
Units: kg			
median	79.8		
full range (min-max)	46.6 to 138.2	-	

Subject analysis sets

Subject analysis set title	Analysis Arm
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Subject analysis set type	Full analysis
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Subject analysis set description:

As this is a single arm study, an extra arm is required to be added so that the statistical analysis can be added. This is NOT extra information or an extra arm. There is only one arm for this study. There were only 54 subjects analysed in total

Reporting group values	Analysis Arm		
Number of subjects	54		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	18		
From 65-84 years	36		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
Caucasian			
Height at creening (cm)			
Units: cm			
median			
full range (min-max)			
Weight at Screening			
Units: kg			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description: Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib in patients with metastatic or unresectable RCC	
Subject analysis set title	Analysis Arm
Subject analysis set type	Full analysis
Subject analysis set description: As this is a single arm study, an extra arm is required to be added so that the statistical analysis can be added. This is NOT extra information or an extra arm. There is only one arm for this study. There were only 54 subjects analysed in total	

Primary: Progression Free Rate at 4 Months

End point title	Progression Free Rate at 4 Months
End point description: Progression Free-Rate at 4 months (i.e. completion of 4 months of treatment, with no disease progression at 8 weeks, and no evidence to suggest progression before the 4-month time-point). The PFS Rate was 23 Patients of 46 evaluable patients (50%) with a 95% CI. Simon's two-stage design required 25 of a planned 43 evaluable patients (50%) with a 95% CI. Simon's two-stage design requires 25 of a planned 43 evaluable patients to be progression free at 4-months in order to reject a PFS rate of 45%, so this unacceptable rate cannot be rejected. Progression Free = Complete Response (0 Patients) + Partial Response (7 Patients) + Stable Disease (16 Patients). As a check on robustness, the analysis was repeated for the Safety Set (all available data for the primary endpoint). The PFS rate was 24 patients of 48 patients (50.0%), with a 95% CI of [36.4 – 63.6]. This PFS rate also means that an unacceptable rate of 45% cannot be rejected.	
End point type	Primary
End point timeframe: From Time of Treatment Start Until 4 Months After Treatment start	

End point values	Single Arm	Analysis Arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46 ^[1]		
Units: Patients				
number (confidence interval 95%)				
Progression Free Rate at 4 Months	50 (36.1 to 63.9)	50 (36.1 to 63.9)		

Notes:

[1] - The statistical arm is being used as it is a single arm study. Only 46 subjects were analysed total

Statistical analyses

Statistical analysis title	Progression-free survival rate at 4 months
Statistical analysis description: Progression-free survival rate	
Comparison groups	Single Arm v Analysis Arm

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other ^[2]
Method	PFS Rate & CI
Parameter estimate	Progression-free survival rate
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.1
upper limit	63.9

Notes:

[2] - Progression-free survival rate and confidence interval

Secondary: Median Time to Progression Free Survival (PFS)

End point title	Median Time to Progression Free Survival (PFS)
End point description:	
Progression-free survival, defined as the length of time between the date of starting treatment and the earliest date of disease progression or death due to any cause. A total of 43 Patients (out of 48 - 89.6%) progressed on study treatment including 3 patients who discontinued study treatment for reason of clinical progression.	
End point type	Secondary
End point timeframe:	
Date of Starting Treatment and earliest date of disease progression or death due to any cause	

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Months				
number (confidence interval 95%)				
Median Time to Progression	4.76 (3.68 to 5.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
End point description:	
Overall response rate (ORR), defined as the percentage of patients who achieved at least a partial response. It is Patients who had complete response + Partial Response.	
End point type	Secondary
End point timeframe:	
From start of study treatment until partial/complete response	

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients				
number (confidence interval 95%)				
Best Response During Study Treatment	22.9 (13.3 to 36.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival, defined as the length of time between the date of starting treatment and the date of death due to any cause. A total of 47 deaths (87.0%) were reported during the study, with median overall survival time of 19.1 months and an accompanying 95% CI of [10.5 – 26.5].

Cause of death was disease progression in all cases except for one patient whose cause of death was an AE related to a new anti-cancer treatment for disease progression.

End point type	Secondary
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End point timeframe:

Date of starting treatment and the date of death due to any cause

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	47 ^[3]			
Units: Months				
number (confidence interval 95%)				
Median Time to Death	19.1 (10.5 to 26.5)			

Notes:

[3] - 47 deaths were reported

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs meeting serious criteria were reported up to 30 days after last dose of IMP. AEs or SAEs after 30 days of active follow up deemed to be causally related to IMP during study was forwarded to CTI

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Single Arm
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Reporting group description:

Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 54 (29.63%)		
number of deaths (all causes)	47		
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Upper			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vomiting			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mobility decreased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pain in lumps in neck and back (soft tissue metastases)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
New lt buttock lump soft tissue metastasis/nodule)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vascular disorders			
Increase tsh			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	24 / 54 (44.44%)		
occurrences (all)	34		
Hypotension			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	7		
Surgical and medical procedures			
Dental extraction gum			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Tooth removed subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Dental extraction subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Spinal fusion surgery subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Shoulder replacement subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
General disorders and administration site conditions Malignant pyrexia subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Fatigue subjects affected / exposed occurrences (all)	29 / 54 (53.70%) 41		
Lump in right forearm appears larger subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Tenderness in both feet subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Bilateral leg oedema scattered subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Pyrexia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 4		
Feeling cold subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Swelling rt groin			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pitting oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Left sided pain radiating to back			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Bipedal oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
chest pain			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Left calf swelling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Inflammation of left arm post aredia iv			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Mucositis			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Blood discharge from penis subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Swollen penis subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Testicular pain subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Intermittant scrotal rash subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Respiratory, thoracic and mediastinal disorders			
Crepes left upper lobe subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Productive cough subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Sore throat subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4		
Cough subjects affected / exposed occurrences (all)	8 / 54 (14.81%) 11		
Post nasal drip subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Epistaxis subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Sob on exertion subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Runny nose			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Shortness of breath on exertion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	7		
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Wheezes/crackles in right lower base lung			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Bilateral pulmonary embolism			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pleuretic chest pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hoarse voice			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Blocked nose subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Insomnia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Anxiety subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Confusion subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Low mood subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Hallucinations subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Investigations Weight Loss subjects affected / exposed occurrences (all)	9 / 54 (16.67%) 19		
hypokalemia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 3		
Raised bilirubin subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Raised upc subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Increase in bp			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Alkaline phosphatase increase			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	4		
Raised alt			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Weight gain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Raised creatinine			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	17		
Ldh increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Glucose increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	3		
Albumin decrease			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Phosphate decrease			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	3		
Rising grade 3 gamma gt			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Decreased magnesium			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Decreased neutrophilis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Platlets decrease			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sodium increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Raised crp			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pleurisy			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Alt increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypophosphatemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Abnormal ecg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Pseudoaneurysm			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Wound bleeding lesion left ring finger			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Right leg pain post op			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Incisional hernia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain (hernia repair site			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 54 (1.85%)</p> <p>1</p> <p>1 / 54 (1.85%)</p> <p>2</p>		
<p>Congenital, familial and genetic disorders</p> <p>Incidental finding of pfo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 54 (1.85%)</p> <p>1</p>		
<p>Cardiac disorders</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bradycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asymptomatic lvef</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 54 (1.85%)</p> <p>1</p> <p>2 / 54 (3.70%)</p> <p>2</p> <p>1 / 54 (1.85%)</p> <p>1</p>		
<p>Nervous system disorders</p> <p>Headaches</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Light headedness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Taste disturbance</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral neuropathy intermittent</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Memory impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Burning sensation feet</p>	<p>17 / 54 (31.48%)</p> <p>20</p> <p>2 / 54 (3.70%)</p> <p>2</p> <p>3 / 54 (5.56%)</p> <p>3</p> <p>1 / 54 (1.85%)</p> <p>1</p> <p>1 / 54 (1.85%)</p> <p>1</p>		

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Sensory neuropathy (fingers)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Spinal cord compression			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vasovagal event			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Restless leg syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Worsening anemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	8		
Iliac lymphadenopathy			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hearing loss			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Right ear pain			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ear disorder			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Eye disorders			
Watery eyes			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vitreous hemorrhages			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cyst eye			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain in right eye secondary to shingles			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vision disturbance (flashing)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Mild periorbital oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Visual disturbance			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal cramps			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Heartburn			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pain in right side abdomen			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	24 / 54 (44.44%)		
occurrences (all)	74		
Abdominal pain			
subjects affected / exposed	10 / 54 (18.52%)		
occurrences (all)	11		
Abdominal discomfort			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Tender abdomen			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	15 / 54 (27.78%)		
occurrences (all)	22		
Ruq tendernes			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	17 / 54 (31.48%)		
occurrences (all)	29		
Gastric reflux			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	13 / 54 (24.07%)		
occurrences (all)	19		
Abdominal bloating			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dry mouth			

subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Pancreatitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain abdomen			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Abdominal soreness (gastric pain)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Esophagitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Palpation soreness epigastric			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Belching			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sore on lips			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Tongue sensitivity			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sluggish bowel			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Discomfort right upper quadrant			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Pain ruq			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastroesophageal reflux			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Anal pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomach rumbling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Upset stomach			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin discolouration nipple area			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hair colour change			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	9		
Small erythematous lesions			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dry skin on face			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Dry skin on hands			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Yellow discolouration of skin			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Dry skin on feet			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Painful callus r foot			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hfsr			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Palm rash			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin rash allergy			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urticaria skin rash bilateral arms and			

legs			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urticaria to bilateral arms and 2 [degree] to bites			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Rash with itch			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Skin rash			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Worsening rash (likely cutaneous lupus)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Scalp rash			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Plantar palmar syndrome			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	6		
Skin change			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Facial Rash			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Hyperkeratosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin lesion behind (l) ear lobe			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Seborrheic dermatitis - face			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin changes-facial redness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Renal and urinary disorders			
Increase in urine output			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urinary frequency increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urinary urgency			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Urine discoloration			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urine disorders (bilirubin ++)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	14 / 54 (25.93%)		
occurrences (all)	18		
Ankle Swelling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Calf cramp			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain right foot			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain right pelvis +leg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Arthralgia right hip			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
General weakness in leg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Shoulder pain			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Reduced mobility			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Painful r foot			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Painful lump in inner groin			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Leg & feet cramps intermittent			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Leg cramps			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
groin pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Lower limb pain at night			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pain jaw			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Pain lower limb			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain lower back			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pain to r heel			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Back ache			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ganglion left wrist			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Lesion to forehead worsening. lytic lesion (skull)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Left groin discomfort			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
hip pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Red tender sides of feet			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Lower rib pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Rt axilla pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Rt scapular pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Osteonecrosis of the jaw			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain left knee			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Supraspinatus tendonitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

groin tenderness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
General joint stiffness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sore right foot			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sore toe			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain in upper right arm			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infections and infestations			
Oral thrush			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Chest infection			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	6		
Head cold			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Lrti (slight wheeze + Cough			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Nasal candidiasis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Candidiasis r axilla			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Flu			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Viral cold			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Buttock abscess			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Glass density in both lungs			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cutaneous fungal infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Shingles			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Leg ulcer infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Rti respiratory tract infection			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	6		
Cold sore			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bronchitis			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Left basal pneumonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infected right tonsil			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	13		
Hyponatremia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Cachectic			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain rt shoulder			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Appetite decrease			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Hyperphosphatemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypermagnesemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		

Hypercalcaemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Hyperkalemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Diabetes worsened			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2011	<p>Original Approved Protocol was Protocol V1.0 04Oct2010. It was updated to Protocol V2.0 02Feb2011, but these were non substantial amendments (to edit Data Management procedures for the study including change of group statistician details & some admin changes). This update was submitted with the amendment for Protocol V3.0 21 June 2011.</p> <p>Protocol V3.0 was updated for a number of reasons including to correct requirements for BP levels, changes to Inclusion/Exclusion Criteria/addition of PI at site & removal of a site, Inclusion of planned analysis for the secondary efficacy endpoints, admin changes.</p> <p>Protocol V3.0 was not approved by the Irish Reg Authorities as they requested that a sentence needed to be added regarding Inclusion Criteria after the text on Sunitinib toxicity and eligibility - 'The Investigator should be aware of the patient's Intolerance/Toxicity with prior sunitinib treatment and take this into account when assessing eligibility'.</p> <p>This update resulted in Protocol V4.0 13-Sept-2011 which was approved.</p>
08 October 2013	<p>Protocol Version 5.0 11-Mar-2013: Principal Changes are:</p> <ul style="list-style-type: none">- Requirement for an extra safety visit to assess liver function at week 6 added in response to updated safety info for pazopanib issued via Dear Investigator Letter.- Change in frequency of CT scans after the 24 week time-point to every 12 weeks (from every 8 weeks) which is in line with Standard of Care- Clarification that Dose Modifications for the managing of treatment related AEs are mandatory as opposed to recommended.- Added recommendations on the use medications that increase gastric pH (PPIs and H2-receptor antagonists) as per IB V10- Clarification in the working of primary & secondary endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported