Clinical trial results:
A Rollover Protocol to allow continued access to Tivozanib Hydrochloride (AV-951) for subjects enrolled in other Tivozanib Hydrochloride Protocols

Summary

EudraCT number	2009-013407-66
Trial protocol	DE NL BE IT GB FR HU BG PL
Global end of trial date	23 June 2015

Results information

Result version number	v1 (current)
This version publication date	27 August 2021
First version publication date	27 August 2021

Trial information

Trial identification

Sponsor protocol code	AV-951-09-901

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01369433
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AVEO Pharmaceuticals, Inc.
Sponsor organisation address	30 Winter Street, Boston, United States, MA 02108
Public contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 857 400-0101, clinical@aveooncology.com
Scientific contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 857 400-0101, clinical@aveooncology.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2015
Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To allow access to tivozanib hydrochloride for subjects who have participated in other tivozanib hydrochloride (monotherapy, combination or crossover) protocols, who are tolerating study drug and displaying clinical benefit.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2010
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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	United States: 124
Worldwide total number of subjects	225
EEA total number of subjects	14

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)	129
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who met all the inclusion and none of the exclusion criteria were enrolled at 83 sites. This study had subjects rolled over from other closed AVEO studies (monotherapy, combination, or crossover) who were tolerating study drug and experiencing clinical benefits.

Pre-assignment

Screening details:

All subjects underwent inclusion and exclusion criteria assessment and all eligible subjects signed the informed consent before undergoing any study related procedures. All the study assessments were performed as per the schedule of assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Monotherapy

Arm description:

Subjects received oral tivozanib hydrochloride at the same dose and schedule as during the parent protocols. Studies under monotherapy were AV-951-10-112, AV-951-07-201, AV-951-10-202, AV-951-12-205, and AV-951-09-902. Drug: Tivozanib hydrochloride.

Arm type	Experimental
Investigational medicinal product name	Tivozanib hydrochloride
Investigational medicinal product code	
Other name	Tivozanib Hydrochloride Monohydrate; KRN951; Ki9294; AV-951
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received 1.0 or 1.5 mg tivozanib capsules once daily for 3 weeks, followed by 1 week off.

Arm title	Combination Therapy

Arm description:

Subjects who were receiving tivozanib hydrochloride combination, continued the combination therapy, as long as it was tolerated, at the same dose and schedule as in the parent protocol. Eligible subjects who received sorafenib in Parent Study AV-951-09-902 at the time of study termination and who rolled into Study AV-951-09-901 began tivozanib hydrochloride at a dose of 1.5 mg/day. Studies under combination therapy were AV-951-07-102, AV-951-07-103, AV-951-08-104, AV-951-10-114, and AV-951-12-204. Combination Drugs: Tivozanib hydrochloride + temsirolimus, Tivozanib hydrochloride + paclitaxel, and Tivozanib hydrochloride + capecitabine.

Arm type	Experimental
Investigational medicinal product name	Tivozanib hydrochloride, temsirolimus, paclitaxel, capecitabine
Investigational medicinal product code	
Other name	Tivozanib hydrochloride, temsirolimus, paclitaxel, capecitabine
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Tivozanib + temsirolimus: Subjects received 0.5 mg, 1.0 mg or 1.5 mg of tivozanib once daily for 3 weeks, followed by 1 week off. On days when tivozanib and temsirolimus were co-administered, tivozanib was administered immediately following temsirolimus infusion. Subjects received 15 mg or 25 mg temsirolimus intravenous (IV) once weekly.

Tivozanib + paclitaxel: Subjects continued to receive 0.5 mg, 1.0 mg, or 1.5 mg of tivozanib once daily for 3 weeks, beginning on Day 1, followed by 1 week off treatment. On days when paclitaxel and tivozanib are co-administered, tivozanib will be administered immediately following the end of the paclitaxel infusion. Subjects received IV paclitaxel 90 mg/m2, administered over 1 hour once a week for 3 weeks, followed by 1 week off.

Tivozanib + capecitabine: Subjects received 1.5 mg of tivozanib once daily for 2 weeks, followed by 1 week off. Subjects received capecitabine twice daily for 2 weeks, beginning on Day 1, followed by 1 week off.

Number of subjects in period 1	Monotherapy	Combination Therapy
Started	209	16
Completed	0	0
Not completed	209	16
Consent withdrawn by subject	5	2
Physician decision	6	1
Study terminated by Sponsor	67	-
Not Progressive Disease	8	-
Death	5	-
Progressive Disease	92	12
Non-compliance	1	-
Adverse event	23	1
Lost to follow-up	1	-
Required significant surgical procedure	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Monotherapy
Reporting group description:	
Subjects received oral tivozanib hydrochloride at the same dose and schedule as during the parent protocols. Studies under monotherapy were AV-951-10-112, AV-951-07-201, AV-951-10-202, AV-951-12-205, and AV-951-09-902. Drug: Tivozanib hydrochloride.	
Reporting group title	Combination Therapy
Reporting group description:	
Subjects who were receiving tivozanib hydrochloride combination, continued the combination therapy, as long as it was tolerated, at the same dose and schedule as in the parent protocol. Eligible subjects who received sorafenib in Parent Study AV-951-09-902 at the time of study termination and who rolled into Study AV-951-09-901 began tivozanib hydrochloride at a dose of 1.5 mg/day. Studies under combination therapy were AV-951-07-102, AV-951-07-103, AV-951-08-104, AV-951-10-114, and AV-951-12-204. Combination Drugs: Tivozanib hydrochloride + temsirolimus, Tivozanib hydrochloride + paclitaxel, and Tivozanib hydrochloride + capecitabine.	

Reporting group values	Monotherapy	Combination Therapy	Total
Number of subjects	209	16	225
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)	122	7	129
From 65-84 years	87	9	96
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	80	6	86
Male	129	10	139

End points

End points reporting groups

Reporting group title	Monotherapy
Reporting group description:	
Subjects received oral tivozanib hydrochloride at the same dose and schedule as during the parent protocols. Studies under monotherapy were AV-951-10-112, AV-951-07-201, AV-951-10-202, AV-951-12-205, and AV-951-09-902. Drug: Tivozanib hydrochloride.	
Reporting group title	Combination Therapy
Reporting group description:	
Subjects who were receiving tivozanib hydrochloride combination, continued the combination therapy, as long as it was tolerated, at the same dose and schedule as in the parent protocol. Eligible subjects who received sorafenib in Parent Study AV-951-09-902 at the time of study termination and who rolled into Study AV-951-09-901 began tivozanib hydrochloride at a dose of 1.5 mg/day. Studies under combination therapy were AV-951-07-102, AV-951-07-103, AV-951-08-104, AV-951-10-114, and AV-951-12-204. Combination Drugs: Tivozanib hydrochloride + temsirolimus, Tivozanib hydrochloride + paclitaxel, and Tivozanib hydrochloride + capecitabine.	

Primary: Number of Subjects With Adverse Events (AEs) and Serious AEs

End point title	Number of Subjects With Adverse Events (AEs) and Serious AEs[1]
End point description:	
Safety and tolerability were assessed in accordance to the protocol of the parent study in which the subjects had participated, before enrolling in the AV-951-09-901 rollover study.	
End point type	Primary
End point timeframe:	
24 Months	

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: There was no statistical analysis planned for this endpoint.

End point values	Monotherapy	Combination Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	16		
Units: number of subjects				
AEs	178	16		
Treatment-related AEs	159	15		
AEs ≥Grade 3 toxicity	111	12		
AEs-study drug interruption	54	6		
AEs-study drug dose reduction	13	0		
AEs-discontinuation of study drug	31	1		
AEs-death	13	1		
Serious Adverse events (SAEs)	44	5		
SAEs ≥Grade 3 toxicity	38	5		
Serious treatment-related AEs	16	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Monotherapy

Reporting group description:

Subjects received oral tivozanib hydrochloride at the same dose and schedule as during the parent protocol. Studies under monotherapy were AV-951-10-112, AV-951-07-201, AV-951-110-202, AV-951-12-205, and AV-951-09-902. Drug: Tivozanib hydrochloride.

Reporting group title	Combination Therapy

Reporting group description:

Subjects who were receiving tivozanib hydrochloride combination, continued the combination therapy, as long as it was tolerated, at the same dose and schedule as in
the parent protocol. Eligible subjects who received sorafenib in Parent Study AV-951-09-902 at the time of study termination and who rolled into Study AV-951-09-901 began tivozanib hydrochloride at a dose of 1.5 mg/day. Studies under combination therapy were AV-951-07-102, AV-951-07-103, AV-951-08-104, AV-951-10-114, and AV-951-12-204. Combination Drugs: Tivozanib hydrochloride + temsirolimus, Tivozanib hydrochloride + paclitaxel, and Tivozanib hydrochloride + capecitabine.

Serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 209 (21.05%)	5 / 16 (31.25%)	
number of deaths (all causes)	13	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			

subjects affected / exposed	2 / 209 (0.96%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Fatigue			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 209 (2.39%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 209 (2.39%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 209 (0.96%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 209 (1.44%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 209 (0.96%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periproctitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 209 (0.96%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 209 (1.44%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	7 / 209 (3.35%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	4 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypochloraemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 209 (0.48%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 209 (82.30%)	16 / 16 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Flushing			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Hypertension			
subjects affected / exposed	88 / 209 (42.11%)	8 / 16 (50.00%)	
occurrences (all)	145	10	
Vena cava thrombosis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 209 (9.09%)	2 / 16 (12.50%)	
occurrences (all)	36	2	
Early satiety			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	81 / 209 (38.76%)	13 / 16 (81.25%)	
occurrences (all)	210	28	
Impaired healing			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Non-cardiac chest pain			
subjects affected / exposed	11 / 209 (5.26%)	1 / 16 (6.25%)	
occurrences (all)	27	1	
Oedema peripheral			
subjects affected / exposed	17 / 209 (8.13%)	5 / 16 (31.25%)	
occurrences (all)	19	5	
Pain			
subjects affected / exposed	14 / 209 (6.70%)	1 / 16 (6.25%)	
occurrences (all)	18	2	
Pyrexia			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Breast mass			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Choking sensation			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	28 / 209 (13.40%)	4 / 16 (25.00%)	
occurrences (all)	36	6	
Dysphonia			
subjects affected / exposed	51 / 209 (24.40%)	4 / 16 (25.00%)	
occurrences (all)	103	5	
Dyspnoea			
subjects affected / exposed	25 / 209 (11.96%)	4 / 16 (25.00%)	
occurrences (all)	38	5	
Epistaxis			
subjects affected / exposed	9 / 209 (4.31%)	2 / 16 (12.50%)	
occurrences (all)	18	2	
Hiccups			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	5 / 209 (2.39%)	1 / 16 (6.25%)	
occurrences (all)	5	1	
Nasal ulcer			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	19 / 209 (9.09%)	1 / 16 (6.25%)	
occurrences (all)	22	1	
Pleuritic pain			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 209 (8.61%)	2 / 16 (12.50%)	
occurrences (all)	23	2	
Depression			
subjects affected / exposed	11 / 209 (5.26%)	2 / 16 (12.50%)	
occurrences (all)	11	2	
Insomnia			
subjects affected / exposed	16 / 209 (7.66%)	2 / 16 (12.50%)	
occurrences (all)	16	2	

Withdrawal syndrome			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Aspartate aminotransferase decreased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 209 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	5 / 209 (2.39%)	2 / 16 (12.50%)	
occurrences (all)	5	2	
Blood uric acid increased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Carbon dioxide increased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 209 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	9 / 209 (4.31%)	1 / 16 (6.25%)	
occurrences (all)	16	1	

Liver function test abnormal			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Low density lipoprotein increased			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Neutrophil count decreased			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	4	2	
Protein total decreased			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	0 / 209 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	4	
Weight decreased			
subjects affected / exposed	31 / 209 (14.83%)	3 / 16 (18.75%)	
occurrences (all)	40	6	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	25 / 209 (11.96%)	2 / 16 (12.50%)	
occurrences (all)	39	3	
Dizziness postural			
subjects affected / exposed	4 / 209 (1.91%)	1 / 16 (6.25%)	
occurrences (all)	5	1	

Dysgeusia			
subjects affected / exposed	14 / 209 (6.70%)	3 / 16 (18.75%)	
occurrences (all)	16	3	
Headache			
subjects affected / exposed	42 / 209 (20.10%)	4 / 16 (25.00%)	
occurrences (all)	68	7	
Hyperaesthesia			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 209 (3.83%)	6 / 16 (37.50%)	
occurrences (all)	12	9	
Peroneal nerve palsy			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vocal cord paralysis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 209 (5.26%)	2 / 16 (12.50%)	
occurrences (all)	28	14	
Leukopenia			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	2 / 209 (0.96%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	6 / 209 (2.87%)	4 / 16 (25.00%)	
occurrences (all)	11	47	
Eye disorders			

Cataract			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Eye swelling			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	2 / 209 (0.96%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Visual impairment			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	7 / 209 (3.35%)	1 / 16 (6.25%)	
occurrences (all)	8	1	
Abdominal mass			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	25 / 209 (11.96%)	4 / 16 (25.00%)	
occurrences (all)	47	6	
Abdominal pain upper			
subjects affected / exposed	17 / 209 (8.13%)	1 / 16 (6.25%)	
occurrences (all)	30	1	
Abdominal tenderness			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	22 / 209 (10.53%)	3 / 16 (18.75%)	
occurrences (all)	26	4	
Diarrhoea			
subjects affected / exposed	87 / 209 (41.63%)	8 / 16 (50.00%)	
occurrences (all)	352	16	
Dry mouth			

subjects affected / exposed	15 / 209 (7.18%)	1 / 16 (6.25%)		
occurrences (all)	42	1		
Dyspepsia				
subjects affected / exposed	25 / 209 (11.96%)	3 / 16 (18.75%)		
occurrences (all)	52	3		
Epigastric discomfort				
subjects affected / exposed	0 / 209 (0.00%)	2 / 16 (12.50%)		
occurrences (all)	0	2		
Gastrointestinal sounds abnormal				
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	2		
Gastrooesophageal reflux disease				
subjects affected / exposed	13 / 209 (6.22%)	0 / 16 (0.00%)		
occurrences (all)	14	0		
Haematochezia				
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)		
occurrences (all)	1	1		
Nausea				
subjects affected / exposed	53 / 209 (25.36%)	8 / 16 (50.00%)		
occurrences (all)	105	13		
Oral pain				
subjects affected / exposed	11 / 209 (5.26%)	0 / 16 (0.00%)		
occurrences (all)	18	0		
Rectal haemorrhage				
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)		
occurrences (all)	1	4		
Small intestinal haemorrhage				
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Stomatitis				
subjects affected / exposed	25 / 209 (11.96%)	5 / 16 (31.25%)		
occurrences (all)	55	9		
Tongue ulceration				
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)		
occurrences (all)	1	1		
Toothache				

subjects affected / exposed	3 / 209 (1.44%)	2 / 16 (12.50%)	
occurrences (all)	5	2	
Vomiting			
subjects affected / exposed	28 / 209 (13.40%)	5 / 16 (31.25%)	
occurrences (all)	57	8	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	2 / 209 (0.96%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Gallbladder enlargement			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 209 (0.96%)	2 / 16 (12.50%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Alopecia			
subjects affected / exposed	7 / 209 (3.35%)	2 / 16 (12.50%)	
occurrences (all)	7	2	
Dry skin			
subjects affected / exposed	9 / 209 (4.31%)	3 / 16 (18.75%)	
occurrences (all)	10	3	
Ecchymosis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Hyperkeratosis			

subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Nail discolouration			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Nail disorder			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Neurodermatitis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Onychoclasis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	26 / 209 (12.44%)	5 / 16 (31.25%)	
occurrences (all)	85	5	
Pruritus			
subjects affected / exposed	8 / 209 (3.83%)	2 / 16 (12.50%)	
occurrences (all)	16	2	
Pruritus generalised			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	2	2	
Psoriasis			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	9 / 209 (4.31%)	1 / 16 (6.25%)	
occurrences (all)	13	5	
Rash erythematous			
subjects affected / exposed	1 / 209 (0.48%)	5 / 16 (31.25%)	
occurrences (all)	1	5	
Rash pruritic			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	5	2	

Skin exfoliation			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 209 (2.39%)	1 / 16 (6.25%)	
occurrences (all)	10	1	
Nocturia			
subjects affected / exposed	1 / 209 (0.48%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Proteinuria			
subjects affected / exposed	18 / 209 (8.61%)	3 / 16 (18.75%)	
occurrences (all)	44	5	
Renal failure			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Urethral atrophy			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	35 / 209 (16.75%)	3 / 16 (18.75%)	
occurrences (all)	37	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 209 (14.83%)	3 / 16 (18.75%)	
occurrences (all)	45	8	
Arthritis			
subjects affected / exposed	1 / 209 (0.48%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	27 / 209 (12.92%)	2 / 16 (12.50%)	
occurrences (all)	36	2	

Joint swelling			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	13 / 209 (6.22%)	4 / 16 (25.00%)	
occurrences (all)	15	5	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 209 (1.91%)	2 / 16 (12.50%)	
occurrences (all)	4	2	
Musculoskeletal pain			
subjects affected / exposed	9 / 209 (4.31%)	2 / 16 (12.50%)	
occurrences (all)	11	2	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 209 (0.48%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Myalgia			
subjects affected / exposed	10 / 209 (4.78%)	1 / 16 (6.25%)	
occurrences (all)	11	1	
Neck pain			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	27 / 209 (12.92%)	3 / 16 (18.75%)	
occurrences (all)	74	3	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Folliculitis			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	6	1	
Infected cyst			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Influenza			

subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Liver abscess			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	8 / 209 (3.83%)	1 / 16 (6.25%)	
occurrences (all)	11	1	
Oral herpes			
subjects affected / exposed	3 / 209 (1.44%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Tinea cruris			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	16 / 209 (7.66%)	0 / 16 (0.00%)	
occurrences (all)	21	0	
Urinary tract infection			
subjects affected / exposed	13 / 209 (6.22%)	3 / 16 (18.75%)	
occurrences (all)	17	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 209 (22.97%)	6 / 16 (37.50%)	
occurrences (all)	87	6	
Dehydration			
subjects affected / exposed	11 / 209 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	17	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	5 / 209 (2.39%)	1 / 16 (6.25%)	
occurrences (all)	8	1	

Hyperkalaemia			
subjects affected / exposed	13 / 209 (6.22%)	0 / 16 (0.00%)	
occurrences (all)	24	0	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 209 (0.96%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Hypoalbuminaemia			
subjects affected / exposed	4 / 209 (1.91%)	1 / 16 (6.25%)	
occurrences (all)	7	1	
Hypocalcaemia			
subjects affected / exposed	4 / 209 (1.91%)	1 / 16 (6.25%)	
occurrences (all)	14	1	
Hypokalaemia			
subjects affected / exposed	11 / 209 (5.26%)	1 / 16 (6.25%)	
occurrences (all)	24	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2009	• Removed objective "to determine overall survival (OS) of subjects treated on tivozanib protocols." • Timings of sample collection (hematology, serum chemistries, urinalysis) updated to "on the first day of Cycle 1 and on the first day of odd numbered cycles thereafter (Cycle 3, Cycle 5, etc.)." • Clarified that laboratory values were be collected on the appropriate CRF page and that clinically significant changes (CS) reported as AEs were to be noted as CS on the appropriate CRF page. • A new section "7.1.10 Concomitant Medications" was added to clarify the collection of concomitant medications.
16 November 2010	• Description of Day 1 assessments was updated in line with Table 1. • Exclusion criterion #4 was changed to systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg • A new criterion was added "newly identified CNS malignancies or documented progression of CNS metastases; subjects will be allowed only if the CNS metastases have been adequately treated with radiotherapy or surgery. For subjects receiving steroid therapy please refer to protocol for allowed steroid maintenance therapy" • Timing of safety monitoring was specified on Day 1 of every cycle. Tivozanib (plus combination agent, if applicable) was added to the data to be monitored. • Added Study Drug Diary, column for Unscheduled Visits, and Disease Assessment footnotes #4 and #5 under Schedule of Events section. • Reference to minimum allowed doses was deleted under rationale for the dose section. • Clarified that 4 weeks following treatment is measured from 30 days after the last dose of tivozanib. • The timing of hematology, chemistries, and urinalysis assessments was updated to "on Day 1 of Cycle 1 and odd numbered cycles". • The window for performing urine or serum pregnancy test was extended to 7 days. • The start of each cycle was clarified to mean Day 1. • The window for performing the pregnancy test at Screening was extended to 7 days. • Clarified that study visit is to occur on Day 1 of every cycle. Study drug administration was clarified to include combination therapy, if applicable. • Cycle numbers of odd-numbered cycles were added. Added the window for performing the End-of-Treatment visit after starting alternative therapy. • The timeframe for collection of adverse events information was changed from "1 month" to "30 days".

11 October 2012	• Changed tivozanib to tivozanib hydrochloride throughout. • Trial objectives and purpose section updated to clarify that protocol AV-951-12-205 was a crossover study and subjects from that study would roll over into protocol AV-951-09-901. • Subject enrollment section was updated to clarify that Interactive Web Response System (IWRS) was implemented for enrollment and management of clinical supplies. • Inclusion criterion #2 was revised to "If female and of childbearing potential, documentation of negative pregnancy test prior to enrollment (i.e. first dose of tivozanib hydrochloride in this protocol)". • Exclusion criterion #1 was updated to "> 4 weeks since discontinuation of study drug treatment on a previous AVEO sponsored clinical trial". • Information on the procedures/parameters to be measured in the study was revised. In addition, removed statement that waivers will be reviewed and approved by the sponsor. • Information on storage condition requirements and administration of tivozanib hydrochloride was updated. • Information on duration of follow up and management of toxicity were revised.
07 October 2013	• Clarified information on subjects who were eligible for enrollment in the study under study design and plan description. • Inclusion criterion # 1 was revised. • Exclusion criteria # I was modified. • Concomitant medication section was updated to provide clarification to sites regarding medications/treatments that were permitted per the protocol and to provide guidance on other medications/treatments • As a result of tivozanib hydrochloride not receiving FDA approval for the treatment of RCC, Study AV-951·09-901 was modified to provide long-term tivozanib hydrochloride treatment to those subjects who were tolerating and deriving clinical benefit from it and restrict data collection to safety (adverse/serious adverse events) data only. • Frequency of blood pressure was modified based on length of treatment with tivozanib hydrochloride (< 1 year vs. > I year) • Frequency and description of procedure (hematology, serum chemistries, urinalysis) modified based on length of treatment with tivozanib hydrochloride « 1 year vs. > 1 year) • Thyroid function was added to monitor additional safety of tivozanib hydrochloride • Clarified that efficacy data, prior and concomitant medications were no longer recorded. • Updated to provide clarification regarding the optional use and review of the study drug administration diary during the study • Description of visits and procedures to be performed was modified to reflect only AE and SAE data will be collected and clinical evaluations based on duration of treatment (< 1 yr vs. > 1 yr) • Removed assessment of concomitant medications and imaging scan at the end of treatment visit • Clarified that unscheduled visits were to be performed as clinically indicated per the investigator • Modified to remove concomitant medication assessment at the 30 day follow-up visit. • Updated to reflect that no more than 3 cycles (bottles) of tivozanib hydrochloride would be dispensed at a time.

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.

Secondary to a lack of new studies contributing subjects to this rollover Study AV-951-09-901, the sponsor, AVEO Pharmaceuticals Inc., decided to terminate this study.

Notes: