Clinical trial results:
A PHASE 2 RANDOMIZED, DOUBLE-BLIND, CROSSOVER, CONTROLLED, MULTI-CENTER, SUBJECT PREFERENCE STUDY OF TIVOZANIB HYDROCHLORIDE VERSUS SUNITINIB IN THE TREATMENT OF SUBJECTS WITH METASTATIC RENAL CELL CARCINOMA

Summary

EudraCT number	2012-001730-33
Trial protocol	BE IT GB ES DE
Global end of trial date	18 September 2013

Results information

Result version number	v1 (current)
This version publication date	25 August 2021
First version publication date	25 August 2021

Trial information

Trial identification

Sponsor protocol code	AV-951-12-205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01673386
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	05 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare subject treatment preference of tivozanib hydrochloride versus sunitinib.

Protection of trial subjects:

The Investigator submitted this protocol, any protocol modifications, and the subject consent form utilized in this study, to the appropriate IRB or EC for review and approval. All subjects participated in the informed consent process and adequate time was given for each subject to ask questions and make a voluntary decision before enrolling in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2012
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	Spain: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	58
EEA total number of subjects	34

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)	26
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All the subjects were recruited as per the inclusion and exclusion criteria.

Pre-assignment

Screening details:

All screening assessments were performed within 28 days prior to the first dose of study drug.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tivozanib First, Then Sunitinib

Arm description:

Subject randomized to this arm received 1.5 mg oral tivozanib hydrochloride (drug 1) daily on a 3 weeks on/1 week off schedule for 12 weeks, followed by 50 mg oral sunitinib (drug 2) daily on a 4 weeks on/2 weeks off schedule for 12 weeks. There will be a 1-week washout period, in addition to the planned rest week(s) between the 2 treatment periods.

Arm type	Experimental
Investigational medicinal product name	Tivozanib
Investigational medicinal product code	
Other name	Tivozanib Hydrochloride
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tivozanib hydrochloride was administered orally, 1.5 mg/day beginning on Day 1 of Week 1 for those subjects randomized to Arm 1, and Day 1 of Week 14 for those subjects randomized to Arm 2. Subjects received 1 capsule of tivozanib hydrochloride and 1 capsule of placebo daily for 3 weeks followed by 1 week rest period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two capsules of over-encapsulated placebo were administered during the planned rest week(s) in order to maintain the blind.

Arm title	Sunitinib First, Then Tivosanib

Arm description:

Subject randomized to this arm received 50 mg oral sunitinib (drug 1) daily on a 4 weeks on/2 weeks off schedule for 12 weeks, followed by 1.5 mg oral tivozanib hydrochloride (drug 2) daily on a 3 weeks on/1 week off schedule for 12 weeks. There will be a 1-week washout period, in addition to the planned rest week(s) between the 2 treatment periods.

Arm type	Experimental

Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was administered orally, 50 mg/day beginning on Day 1 of Week 14 for those subjects randomized to Arm 1, and Day 1 of Week 1 for those subjects randomized to Arm 2. Subjects received 2 capsules, each 25 mg, of sunitinib daily for 4 weeks followed by a 2 week rest period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two capsules of over-encapsulated placebo were administered during the planned rest week(s) in order to maintain the blind.

Number of subjects in period 1	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib
Started	27	31
Completed	2	4
Not completed	25	27
Consent withdrawn by subject	-	2
Adverse event, non-fatal	5	2
Study terminated by sponsor	16	22
Progressive disease	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	58	58	
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)	26	26	
From 65-84 years	32	32	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.6		
standard deviation	± 9.72	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	48	48	

End points

End points reporting groups

Reporting group title	Tivozanib First, Then Sunitinib

Reporting group description:

Subject randomized to this arm received 1.5 mg oral tivozanib hydrochloride (drug 1) daily on a 3 weeks on/1 week off schedule for 12 weeks, followed by 50 mg oral sunitinib (drug 2) daily on a 4 weeks on/2 weeks off schedule for 12 weeks. There will be a 1-week washout period, in addition to the planned rest week(s) between the 2 treatment periods.

Reporting group title	Sunitinib First, Then Tivosanib

Reporting group description:

Subject randomized to this arm received 50 mg oral sunitinib (drug 1) daily on a 4 weeks on/2 weeks off schedule for 12 weeks, followed by 1.5 mg oral tivozanib hydrochloride (drug 2) daily on a 3 weeks on/1 week off schedule for 12 weeks. There will be a 1-week washout period, in addition to the planned rest week(s) between the 2 treatment periods.

Subject analysis set title	Tivozanib
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects receiving Tivozanib in Arm 1 and Arm 2

Subject analysis set title	Sunitinib
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects receiving Sunitinib in Arm 1 and Arm 2.

Primary: Proportion of Subjects Who Prefer Tivozanib Hydrochloride or Sunitinib

End point title	Proportion of Subjects Who Prefer Tivozanib Hydrochloride or Sunitinib[1]

End point description:

End point type	Primary

End point timeframe:

Up to 25 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated prior to completing enrollment; due to low enrollment, no data was collected/analyzed.

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Subjects				

Notes:

[2] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[3] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With adverse events (AEs) and serious AEs (SAEs)

End point title	Number of Subjects With adverse events (AEs) and serious AEs

	(SAEs)

End point description:

Number of subjects with serious and non-serious adverse events during the study.

End point type	Secondary

End point timeframe:

Up to 25 weeks

End point values	Tivozanib	Sunitinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	41		
Units: Subjects				
number (not applicable)				
At least one AE	35	40		
At least one treatment-related AE	33	38		
At least one SAE	6	7		
At least one treatment-related SAE	1	3		
At least one AE leading to drug withdrawal	3	8		
At least one AE with outcome of death	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Dose Reductions

End point title	Number of Subjects With Dose Reductions

End point description:

End point type	Secondary

End point timeframe:

Up to 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: subjects				
number (not applicable)				

Notes:

[4] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

[5] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Dose Interruptions

End point title	Number of Subjects With Dose Interruptions

End point description:

End point type	Secondary

End point timeframe:

Up to 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: subjects				
number (not applicable)				

Notes:

[6] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[7] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3/4 Hematology Abnormalities

End point title	Number of Subjects With Grade 3/4 Hematology Abnormalities

End point description:

End point type	Secondary

End point timeframe:

Up to 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Subjects				
number (not applicable)				

Notes:

[8] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[9] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3/4 Coagulation Abnormalities

End point title	Number of Subjects With Grade 3/4 Coagulation Abnormalities

End point description:

End point type	Secondary

End point timeframe:

Upto 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Subjects				
number (not applicable)				

Notes:

[10] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[11] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3/4 Urinalysis Abnormalities

End point title	Number of Subjects With Grade 3/4 Urinalysis Abnormalities

End point description:

End point type	Secondary

End point timeframe:

Upto 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Subjects				
number (not applicable)				

Notes:

[12] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[13] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Title Number of Subjects With Grade 3/4 Thyroid Function Abnormalities

End point title	Title Number of Subjects With Grade 3/4 Thyroid Function Abnormalities

End point description:

End point type	Secondary

End point timeframe:

Upto 25 weeks

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Subjects				
number (not applicable)				

Notes:

[14] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[15] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 10, 14, 17, 23, and End of Treatment

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: Subjects				
number (not applicable)				

Notes:

[16] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

[17] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FACT Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS)

End point title	Change From Baseline in FACT Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 10, 14, 17, 23, and End of Treatment

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: scores on scale				
number (not applicable)				

Notes:

[18] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

[19] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Diarrhea (FACT-D)

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Diarrhea (FACT-D)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 10, 14, 17, 23, and End of Treatment

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: scores on scale				
number (not applicable)				

Notes:

[20] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[21] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Euro Quality of Life - 5 Dimensions (EQ-5D)

End point title	Change From Baseline in Euro Quality of Life - 5 Dimensions (EQ-5D)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 10, 14, 17, 23, and End of Treatment

End point values	Tivozanib First, Then Sunitinib	Sunitinib First, Then Tivosanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: scores on scale				
number (not applicable)				

Notes:

[22] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.
[23] - Study was terminated prior to completing enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the ICF until 30 days after permanent treatment discontinuation at Week 25. The Sponsor terminated Study AV-951-12-205 before enrollment was completed, following the negative decision of the US FDA on the NDA (204408).

Adverse event reporting additional description:

MedDra v15.0

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Tivozanib

Reporting group description:

Tivozanib hydrochloride 1.5 mg was administered orally to the randomized subjects first in Arm 1 and second in Arm 2.

Reporting group title	Sunitinib

Reporting group description:

Sunitinib 50 mg was administered orally to the randomized subjects first in Arm 2 and second in Arm 1.

Serious adverse events	Tivozanib	Sunitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	7 / 41 (17.07%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 38 (2.63%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oesophagitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 38 (2.63%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Respiratory Failure			
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Flank Pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	1 / 38 (2.63%)	0 / 41 (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 / 38 (2.63%)	0 / 41 (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: 4 %

Non-serious adverse events	Tivozanib	Sunitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	40 / 41 (97.56%)	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Hypertension			
subjects affected / exposed	19 / 38 (50.00%)	12 / 41 (29.27%)	
occurrences (all)	34	20	
Hypotension			
subjects affected / exposed	3 / 38 (7.89%)	3 / 41 (7.32%)	
occurrences (all)	3	5	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	5 / 38 (13.16%)	9 / 41 (21.95%)	
occurrences (all)	6	13	
Chills			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	14 / 38 (36.84%)	15 / 41 (36.59%)	
occurrences (all)	23	19	
Oedema Peripheral			
subjects affected / exposed	2 / 38 (5.26%)	2 / 41 (4.88%)	
occurrences (all)	2	3	
Peripheral Swelling			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	2 / 38 (5.26%)	4 / 41 (9.76%)	
occurrences (all)	2	4	
Tenderness			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 38 (15.79%)	4 / 41 (9.76%)	
occurrences (all)	6	4	
Dysphonia			
subjects affected / exposed	13 / 38 (34.21%)	5 / 41 (12.20%)	
occurrences (all)	16	5	
Dyspnoea			
subjects affected / exposed	4 / 38 (10.53%)	6 / 41 (14.63%)	
occurrences (all)	5	8	
Epistaxis			
subjects affected / exposed	0 / 38 (0.00%)	6 / 41 (14.63%)	
occurrences (all)	0	6	
Oropharyngeal Pain			

subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Productive Cough			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 41 (2.44%)	
occurrences (all)	2	1	
Investigations			
Amylase Increased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	8	
Blood Creatinine Increased			
subjects affected / exposed	1 / 38 (2.63%)	3 / 41 (7.32%)	
occurrences (all)	1	4	
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)	5 / 41 (12.20%)	
occurrences (all)	0	9	
Weight decreased			
subjects affected / exposed	4 / 38 (10.53%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	3	
Platelet Count Decreased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 38 (7.89%)	3 / 41 (7.32%)	
occurrences (all)	3	3	

Dysgeusia			
subjects affected / exposed	4 / 38 (10.53%)	17 / 41 (41.46%)	
occurrences (all)	4	21	
Headache			
subjects affected / exposed	5 / 38 (13.16%)	0 / 41 (0.00%)	
occurrences (all)	6	0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 38 (2.63%)	3 / 41 (7.32%)	
occurrences (all)	1	4	
Neutropenia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	0 / 38 (0.00%)	5 / 41 (12.20%)	
occurrences (all)	0	6	
Eye disorders			
Eyelid Oedema			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 38 (2.63%)	3 / 41 (7.32%)	
occurrences (all)	1	6	
Abdominal Pain Upper			
subjects affected / exposed	1 / 38 (2.63%)	5 / 41 (12.20%)	
occurrences (all)	1	5	
Constipation			
subjects affected / exposed	5 / 38 (13.16%)	3 / 41 (7.32%)	
occurrences (all)	8	3	
Diarrhoea			

subjects affected / exposed	17 / 38 (44.74%)	15 / 41 (36.59%)	
occurrences (all)	22	19	
Dry Mouth			
subjects affected / exposed	2 / 38 (5.26%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
Dyspepsia			
subjects affected / exposed	2 / 38 (5.26%)	10 / 41 (24.39%)	
occurrences (all)	2	10	
Flatulence			
subjects affected / exposed	1 / 38 (2.63%)	5 / 41 (12.20%)	
occurrences (all)	1	7	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Gingival Pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	4 / 38 (10.53%)	12 / 41 (29.27%)	
occurrences (all)	4	18	
Oral Dysaesthesia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Oral Pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Proctalgia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Rectal Haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	4	
Stomatitis			
subjects affected / exposed	8 / 38 (21.05%)	10 / 41 (24.39%)	
occurrences (all)	10	11	
Vomiting			

subjects affected / exposed	3 / 38 (7.89%)	7 / 41 (17.07%)	
occurrences (all)	5	12	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 38 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 38 (2.63%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Dry Skin			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Hair Colour Changes			
subjects affected / exposed	1 / 38 (2.63%)	6 / 41 (14.63%)	
occurrences (all)	1	7	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	6 / 38 (15.79%)	10 / 41 (24.39%)	
occurrences (all)	10	29	
Pruritus			
subjects affected / exposed	3 / 38 (7.89%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
Rash			
subjects affected / exposed	3 / 38 (7.89%)	4 / 41 (9.76%)	
occurrences (all)	3	6	
Skin Discolouration			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Yellow skin			
subjects affected / exposed	0 / 38 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Proteinuria			

subjects affected / exposed	1 / 38 (2.63%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Back Pain			
subjects affected / exposed	3 / 38 (7.89%)	6 / 41 (14.63%)	
occurrences (all)	5	6	
Muscle Spasms			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Musculoskeletal Pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal Stiffness			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	0 / 38 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Pain In Extremity			
subjects affected / exposed	1 / 38 (2.63%)	2 / 41 (4.88%)	
occurrences (all)	1	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Tooth Infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Urinary Tract Infection			

subjects affected / exposed	2 / 38 (5.26%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	7 / 38 (18.42%)	11 / 41 (26.83%)	
occurrences (all)	12	14	
Hyponatraemia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2012	- Tivozanib was changed to tivozanib hydrochloride. - To clarify rest periods during study drug treatment, "off week treatment period" was changed to planned rest week(s) or planned rest period as appropriate. - Text was added for clarity that any subject permanently discontinuing any further study treatment will have a 30-day post treatment safety visit and that this visit is for assessment of delayed effects of study drugs. - The stratification factors were modified to remove number of metastatic sites (0 and 1 vs 2+) and to add histology (clear cell vs. non-clear cell). - The study population was modified to enroll only those subjects with metastatic renal cell carcinoma who did not receive prior systemic therapy for metastatic disease and not to enroll subjects with locally advanced disease. - Inclusion criterion was modified to remove requirement for prior nephrectomy and to allow subjects with or without prior nephrectomy to enroll. - Treatment with full dose oral anticoagulation was permitted.

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.

The Sponsor terminated Study AV-951-12-205 before enrollment was completed, following the negative decision of the US FDA on the NDA (204408).

Notes: