Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Multi-Center Study Comparing Tivozanib Hydrochloride In Combination With Paclitaxel Versus Placebo In Combination With Paclitaxel in the Treatment of Subjects With Locally Recurrent and/or Metastatic Triple Negative Breast Cancer

Summary

EudraCT number	2012-003507-35
Trial protocol	IT ES
Global end of trial date	13 April 2014

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-951-12-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01745367
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	24 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare progression free survival (PFS) of subjects treated with tivozanib hydrochloride in combination with paclitaxel vs subjects treated with placebo in combination with paclitaxel.

Protection of trial subjects:

Prior to the initiation of the study at each study center, the clinical study protocol, subject information sheet, informed consent form (ICF), and all other relevant study documentation were submitted to and approved by the responsible national Independent Ethics Committee (IEC) / Institutional Review Board (IRB).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 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	United States: 17
Country: Number of subjects enrolled	Bahamas: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Ukraine: 7
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Country: Number of subjects enrolled	Australia: 2
Worldwide total number of subjects	30
EEA total number of subjects	0

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)	24
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who met all the inclusion and none of the exclusion criteria were enrolled.

Pre-assignment

Screening details:

Subjects attended a screening visit maximum of 4 weeks before receiving their first dose. All participants underwent inclusion exclusion criteria assessment and all eligible participants signed the informed consent before undergoing any study-related procedures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo in Combination With Paclitaxel

Arm description:

Participants received placebo orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo matching AV-951
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 1.5 mg placebo orally once daily beginning on Day 1 for 3 weeks followed by 1 week off treatment. One cycle of tivozanib hydrochloride or placebo was defined as 4 weeks.

Arm title	Tivozanib Hydrochloride in Combination With Paclitaxel

Arm description:

Participants received 1.5 mg tivozanib hydrochloride orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.

Arm type	Experimental
Investigational medicinal product name	Tivozanib hydrochloride (AV-951)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 1.5 mg tivozanib hydrochloride orally once daily beginning on Day 1 for 3 weeks followed by 1 week off treatment. One cycle of tivozanib hydrochloride or placebo was defined as 4 weeks.

Number of subjects in period 1	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel
Started	8	22
Treated	8	21
Completed	0	0
Not completed	8	22
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	2
Termination of The Study by The Sponsor	6	18
Other Reasons Unspecified	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo in Combination With Paclitaxel
Reporting group description:	
Participants received placebo orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.	
Reporting group title	Tivozanib Hydrochloride in Combination With Paclitaxel
Reporting group description:	
Participants received 1.5 mg tivozanib hydrochloride orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.	

Reporting group values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel	Total
Number of subjects	8	22	30
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)	4	20	24
From 65-84 years	4	2	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	22	30
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	8	14	22
Black	0	5	5
Asian	0	2	2
Dominican	0	1	1

End points

End points reporting groups

Reporting group title	Placebo in Combination With Paclitaxel
Reporting group description:	
Participants received placebo orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.	
Reporting group title	Tivozanib Hydrochloride in Combination With Paclitaxel
Reporting group description:	
Participants received 1.5 mg tivozanib hydrochloride orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.	

Primary: Comparison of Progression-free Survival (PFS) of Subjects

End point title	Comparison of Progression-free Survival (PFS) of Subjects[1]
End point description:	
PFS is defined as the time from randomization to progressive disease (PD) or death. The PFS comparison was to be performed for subjects treated with tivozanib hydrochloride in combination with paclitaxel vs placebo in combination with paclitaxel.	
End point type	Primary
End point timeframe:	
approximately 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: The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Subjects				
number (not applicable)				

Notes:

[2] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.
[3] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Objective Response Rate (ORR) and Duration of Response (DoR) of Subjects

End point title	Comparison of Objective Response Rate (ORR) and Duration of Response (DoR) of Subjects

End point description:

ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. DoR is defined as the length of time that a tumor continues to respond to treatment without the cancer growing or spreading. The ORR and DoR comparison was to be performed for subjects treated with tivozanib hydrochloride in combination with paclitaxel vs placebo in

combination with paclitaxel.

End point type	Secondary

End point timeframe:

approximately 24 months

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Subjects				
number (not applicable)				

Notes:

[4] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.
[5] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Overall Survival (OS) of Subjects

End point title	Comparison of Overall Survival (OS) of Subjects

End point description:

OS measures how long subjects, who undergo a certain treatment regimen, live compared to subjects who are in a control group (i.e., taking either another drug or an inactive treatment, known as a placebo). OS comparison was to be performed for subjects treated with tivozanib hydrochloride in combination with paclitaxel vs placebo in combination with paclitaxel.

End point type	Secondary

End point timeframe:

approximately 24 months

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Subjects				
number (not applicable)				

Notes:

[6] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.
[7] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability of Tivozanib Hydrochloride in Combination With Paclitaxel vs Placebo in Combination With Paclitaxel

End point title	Safety and Tolerability of Tivozanib Hydrochloride in Combination With Paclitaxel vs Placebo in Combination With Paclitaxel

End point description:

Number of subjects with serious and non-serious adverse events. Descriptive statistical analyses were to be performed for a limited set of data (disposition, demographics, and adverse events).

End point type	Secondary

End point timeframe:

approximately 24 months

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	21		
Units: Subjects				
Subjects with serious adverse events	1	1		
Subjects with non-serious adverse events	8	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of Tivozanib Hydrochloride and Paclitaxel When Administered in Combination

End point title	Pharmacokinetics (PK) of Tivozanib Hydrochloride and Paclitaxel When Administered in Combination

End point description:

PK is defined as the study of the bodily absorption, distribution, metabolism, and excretion of drugs.

End point type	Secondary

End point timeframe:

approximately 24 months

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: not applicable				
number (not applicable)				

Notes:

[8] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

[9] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Identification of Hypoxia Gene Signature

End point title	Identification of Hypoxia Gene Signature

End point description:

Evaluation of hypoxia gene signature as a predictive biomarker of tivozanib hydrochloride response and establish the optimal cut-off to identify biomarker positive and negative subgroups. The genes comprising the hypoxia gene signature was to be analyzed in tumor tissue from subjects.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: Pre-dose and 2, 4 and 24 hours post dose; Cycle 1, Day 8: Predose; Cycle 1, Day 21: Pre-dose and 2, 4, 24, 48, and 96 hours post dose; Cycle 2 (Day 1): Pre-dose

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Subjects				
number (not applicable)				

Notes:

[10] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

[11] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Subjects' Quality of Life (QoL)

End point title	Measurement of Subjects' Quality of Life (QoL)

End point description:

The Functional Assessment of Cancer Therapy-Breast (FACT-B) and Euro Quality of Life - 5 Dimensions (EQ-5D) questionnaires was used throughout the study to measure subjects' health-related QoL.

End point type	Secondary

End point timeframe:
approximately 24 months

End point values	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: score on a scale				
number (not applicable)				

Notes:

[12] - The study was terminated prior to complete enrollment; due to low enrollment, no data was collected.
[13] - The study was terminated prior to complete 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:

14 months

Adverse event reporting additional description:

Serious treatment-emergent adverse events and treatment emergent adverse events in Safety Population was reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo in Combination With Paclitaxel

Reporting group description:

Participants received placebo orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.

Reporting group title	Tivozanib Hydrochloride in Combination With Paclitaxel

Reporting group description:

Participants received 1.5 mg tivozanib hydrochloride orally once daily with 90 mg/m^2 of paclitaxel administered intravenously beginning on Day 1 for 3 weeks followed by 1 week off treatment.

Serious adverse events	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain cancer metastatic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (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			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (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			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo in Combination With Paclitaxel	Tivozanib Hydrochloride in Combination With Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	19 / 21 (90.48%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	7 / 21 (33.33%)	
occurrences (all)	0	8	
Poor venous access			

subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 8 (50.00%)	11 / 21 (52.38%)	
occurrences (all)	6	15	
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	9 / 21 (42.86%)	
occurrences (all)	0	9	
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	6	
Rhinitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Liver function test abnormal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	2	9	
Platelet count increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Laceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Dysgeusia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Headache			
subjects affected / exposed	1 / 8 (12.50%)	4 / 21 (19.05%)	
occurrences (all)	1	8	
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Neuropathy peripheral			
subjects affected / exposed	1 / 8 (12.50%)	5 / 21 (23.81%)	
occurrences (all)	1	6	
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 8 (25.00%)	4 / 21 (19.05%)	
occurrences (all)	3	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 8 (37.50%)	5 / 21 (23.81%)	
occurrences (all)	11	5	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	8	
Neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	8 / 21 (38.10%)	
occurrences (all)	3	17	
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	3 / 8 (37.50%)	6 / 21 (28.57%)	
occurrences (all)	5	6	
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	4 / 8 (50.00%)	9 / 21 (42.86%)	
occurrences (all)	6	12	
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	4	
Stomatitis			

subjects affected / exposed	1 / 8 (12.50%)	6 / 21 (28.57%)	
occurrences (all)	1	7	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	5 / 21 (23.81%)	
occurrences (all)	1	8	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 8 (50.00%)	7 / 21 (33.33%)	
occurrences (all)	5	12	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Pruritis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Pruritis Generalized			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 8 (12.50%)	4 / 21 (19.05%)	
occurrences (all)	1	6	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	0 / 8 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 21 (14.29%)	
occurrences (all)	4	3	

Back Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	1	4	
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Rash pustular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	3 / 21 (14.29%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	5 / 21 (23.81%)	
occurrences (all)	2	7	
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2013	1. Section 5.1, Introduction, Background; Section 5.6 Previous human experience with tivozanib hydrochloride: text in this section was modified to include additional data on other vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors in second line setting. Information regarding rationale for study design was also updated. Pharmacokinetics in subjects with solid tumors section was updated to include more recent data. Order of sections was rearranged. 2. Section 5.7.3, Potential Risks/Benefits of Tivozanib Hydrochloride: Section number has changed from 5.7.4 to 5.7.3. The following text was removed: Tivozanib hydrochloride should not be administered to pregnant women, as it is known that angiogenesis plays an important role in reproductions and embryonic development. It is required that women of childbearing potential undergo a pregnancy test before treatment and must use adequate contraceptive measures while on study and for at least 30 days after the last dose of study drug. 3. Section 6.2, Secondary Objectives: The following objective was removed- to evaluate QoL. 4. Section 8.2, Subject Exclusion Criteria: New exclusion criteria #2 was added as follows: 2. Subjects who have received any prior treatment with any investigational or licensed drug that targets VEGF, VEGFR or the VEGF pathway. 5. Section 8.3, Concomitant Medications and Procedures During the Study Treatment: The following prohibited medication was added: Steroid therapy equivalent to prednisone >10 mg/day and Denosumab is allowed for the prevention of skeletal-related events in subjects with bone metastases.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 January 2014	The Sponsor terminated Study AV-951-12-204 before enrollment was completed after determining that enrollment of subjects was much lower than expected, and that timely completion of the study was not feasible.	-

Notes:

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-951-12-204 before enrollment was completed after determining that enrollment of subjects was much lower than expected, and that timely completion of the study was not feasible.

Notes: